Specific Hypersensitiveness

A. Anaphylaxis—a state of hypersensitiveness produced experimentally in animals by injecting them for the second time with the same protein. The reaction is mediated by an antigen-antibody union and manifests itself in a group of symptoms characteristic for each species.

B. Allergy—the specific hypersensitiveness of human beings. The *shock organ is the skin and mucous membrane. The pathology* is that of edema and possibly smooth-muscle spasm. Signs and symptoms depend on the location of the lesion. Treatment is carried out by the removal of the cause and by "hyposensitization."

I. Familial Allergy or Atopy—a form of allergy associated with the transmission of a sensitive shock organ, and characterized usually by
called reagins.
scratch test. Tl
possible.

A. Clinical conditions included are: hay fever, bronchial asthma, nasal allergy, some cases of eczema of children, atopic dermatitis, urticaria, angioneurotic edema, and migraine.

B. Characterized by:

1. Family history of allergy.
2. Personal history of other allergic manifestations.
3. Eosinophils in the blood, nasal secretions, and sputum.
4. Positive skin or ophthalmic tests, or both.
5. Response to epinephrine.

C. Caused by:

1. Exogenous Agents
   - (a) *Inhalants:* pollen, fungi, animal danders, cosmetics, house dust, occupational dust (flour, ipecac), etc.
   - (b) *Contactants:* clothing, cosmetics, chemicals, drugs, etc.
   - (c) *Ingestants:* egg, milk, cereals, drugs, etc.
   - (d) *Injectants:* serum, insect bites, biologic products (insulin), etc.
   - (e) *Physical agents:* sun, heat, cold, effort.
2. Endogenous Agents
   - (a) *Infestants:* intestinal parasites.
   - (b) *Infectants:* bacteria, fungi.

II. Acquired Allergy.

A. Contact dermatitis may be due to plant oils such as poison ivy, or to heavy metals; industrial dermatoses may be due to a true allergy *or to* local chemical irritation of skin. Mechanism is not known; the diagnostic test is the [illegible] are of no value. [illegible] the elimination [illegible] on of a suitable [illegible] edure may be of value both in the prevention and treatment of conditions such as poison ivy dermatitis.

B. Serum allergy may be either acquired or familial.
   1. Serum sickness: the reaction is not serious; it follows 3 to 12 days after administration of foreign serum for the first time.
   2. Accelerated serum reaction is a form of acquired serum allergy which occurs *without an incubation period*, usually after the administration of a foreign serum for the second time. It is more serious and may prove fatal, especially if serum is given intravenously.
   3. Serum atopy. may be fatal. Always perform an intra- [illegible]

C. Drug allergy may be either acquired or familial. It is caused by the administration of a nontoxic dose of a drug. Examples are: aspirin, quinine, iodides, bromides, [illegible] drug [illegible] are of [illegible] ted by [illegible]

D. Bacterial allergy is a form of sensitiveness *to secretory* products of bacterial growth (tuberculin and fungi). The tuberculin type of skin reaction is diagnostic. The mechanism is not known *Previous infection* with the respective organism is essential in this form of allergy.

E. Physical allergy: heat, light, cold, and *mechanical* irritation (dermographism). Manifestations may be those of urticaria, angioneurotic edema, severe dermatitis, etc. The reaction may also be *atopic*. The mechanism is not known. The diagnostic test is by exposure.

FATAL BRONCHIAL ASTHMA

(Reduced from ×80:
Modified Mallory Aniline-blue Stain)





(Top) Portion of bronchus blocked by mucous plug containing numbers of eosinophils.

(Bottom) Wall of bronchus showing hyaline basement membrane (sharp blue line), infiltration with lymphocytes and eosinophils, hypertrophied muscle, degenerating cartilage, and prominent mucous glands



ESSENTIALS OF ALLERGY

BY

LEO H. CRIEP, M.D.

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WITH A FOREWORD BY

ROBERT A. COOKE, M.D.

Chairman, Committee on Education, American Academy of Allergy

42 Illustrations in Black and White and 1 Plate in Full Color



Philadelphia London Montreal

J. B. LIPPINCOTT COMPANY

SECOND IMPRESSION

Under Government regulations for saving paper during the war the thickness of this book has been reduced below the customary peace time standards The text is complete and unabridged

PRINTED IN THE UNITED STATES OF AMERICA

Foreword

Allergy is one of the most fascinating and intriguing fields of medicine. For the medical student and for the general practitioner alike, it is essential to secure a proper foundation and perspective, for there is today and probably always will be an abundance of loose thinking, talking, and writing. The majority of the practitioners of today never had any formal education in allergy in their student days and the present teaching of this subject even in the best medical schools is scanty at best. This is not to say it should be given a predominating place in training for a medical degree, for it is after all only a part of internal medicine, but it is an important part.

The generally accepted diseases of allergy—asthma, urticaria, vasomotor rhinitis, and the angio-edema group—are important not because they are communicable (for they are not, except perhaps in a genetic sense), and not because of any high mortality, but rather because they are common, because they are persistent, and because they carry a relatively high morbidity rate. In other words, they are what the practitioner will meet in over 10 per cent of his practice, and it will be to his own and to his patients' satisfaction if and when he knows how to recognize and treat them.

Aside from this very practical aspect, allergy derives perhaps its greatest significance and value from the fact that it is being more generally recognized as the satisfactory explanation of certain cellular reactions resulting in reversible and irreversible lesions of diseases not now accepted and classified [illegible]

cert [illegible]

for [illegible] limited to reactions to protein and other inanimate organic material.

It does not belittle our present knowledge of allergy to admit, as we should, that relatively little is known of the fundamentals of the allergic reactions or the nature of the protective response to present-day methods of immunologic treatment which rests largely on empiricism.

But there are certain facts that are known even though much that passes for knowledge is still speculative. That confusion between fact and hypothesis still exists on many points in the minds of many is a natural condition at this stage of the development in the field of allergy But it is highly important to hold this tendency in check, and in this book the author has done just this.

Based upon his long experience in research and clinical allergy, Dr. Criep has presented the existing knowledge of allergy with clarity and precision. He adequately outlines the special technics and emphasizes their limitations. In short, he has adhered strictly to the line between the facts of allergy as they are now interpreted and those fancies that too largely permeate allergy thought, literature, and practice today He has succeeded fully in doing what he set out to do—to write a sound textbook on allergy that should be a joy to the undergraduate students and the general practitioners for whom it is intended.

ROBERT A. COOKE, M.D.

New York

Preface

In the past decade there have been tremendous advances in clinical allergy. Starting as a purely speculative study, this branch of internal medicine has earned a permanent place in the family of medical specialties. This is witnessed by the rapidly accumulating store of medical literature and the appearance of a number of books on the subject; its inclusion in the curriculum of most medical schools; the establishment of well-conducted allergy clinics throughout the country, and by the existence of national societies and national periodicals devoted to research and clinical investigation in allergy. The importance of allergy in the practice of medicine is even more apparent when it is pointed out that 10% of the population show major allergies and that from 30 to 50% manifest some evidence of minor allergies.

This book is meant neither for the specialist in allergy nor for the allergic patient, both of these can find elsewhere suitable literature on the subject. However, it is intended as a manual for the undergraduate medical student as well as for the practicing physician

The undergraduate medical student will be interested during *his* course in Immunology in Part I of the book which deals with the basic immunologic principles of anaphylaxis and allergy. The application of these principles to clinical allergy as covered in Part II will be of value to the student in his clinical years.

For the sake of conciseness and clarity the subject matter is dealt with in outline form. For this reason, extensive discussions and quotations are omitted, since these are often confusing to the beginner and are easily accessible to those whose interest *carries* them deeper into this field. For a similar reason, no attempt is made to engage in

lengthy controversial discussions where more than one view or theory is available in the consideration of a given subject. The divergent views and the principal evidence for and against them are stated briefly. The view which is most readily acceptable is adopted for teaching purposes.

Each chapter is followed by a series of case reports drawn from the writer's practice. These are intended to illustrate essential practical considerations. An effort is thus made to emphasize those diagnostic and therapeutic methods which will be of help in managing allergic patients. No attempt is made to include an extensive bibliography, since this may be found in many of the books listed for reference

In writing this book the author has drawn freely from all the available literature and books on allergy as well as from his own experience. He is therefore deeply grateful to the many unnamed collaborators and investigators whose work and publications have been responsible for our present knowledge of allergy; to the editors and publishers with whose permission certain material is reprinted; and, finally, to those authors whose books are listed at the end of this manual as reference works in Allergy.

The author also wishes to express his thanks to Albert Levin, B.P.A., of the Department of Photography of the Montefiore Hospital, for his help in securing many of the photographs included in the book; to Anne Shiras, B.P.A., and Mortimer Cohen, M D, of the Department of Pathology, School of Medicine, University of Pittsburgh, for the frontispiece, to G. A. Koelsche, M D., of the Mayo Clinic and Mr. O C Durham of the Abbott Laboratories for the tables of distribution of pollens in the United States, to his wife for her untiring efforts and help in the reading of the manuscript and proofs; to his secretary Miss Evelyn Hausman, for the many transcriptions, and to his publishers for their kindness and cooperation

L H C

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1

Hypersensitiveness

NOMENCLATURE
IMMUNE BODIES IN HYPERSENSITIVENESS
CLASSIFICATION
HISTORY
SUMMARY

NOMENCLATURE

As might be expected in the development of a comparatively new study, there exists a great deal of confusion in the literature on allergy. This confusion is due to a variety of terms coined by various workers to denote phenomena observed in experimental and clinical allergy. For this reason it seems advisable to make an attempt to clarify this nomenclature and to indicate the terminology to be adopted in this book.

The term hypersensitiveness is used in an all-inclusive sense to denote a *state* of specific sensitivity on the part of a lower animal or human being to a substance which is harmless to other members of the same species. Thus, an individual is said to be hypersensitive to egg if the ingestion of a small amount of egg gives him unusual symptoms, such as asthma. The terms sensitiveness and sensitivity are used synonymously with hypersensitiveness and hypersensitivity. General usage justifies the employment of the term hypersensitiveness, redundant though it may be.

The sensitivity in these instances is always specific. It results from exposure to a definite substance. An animal sensitive only to egg white will develop manifestations if exposed specifically to egg white alone. These manifesta-

tions are characteristic for a given species. Thus, following exposure to the antigen (exciting agent), a sensitive guinea pig develops a characteristic train of symptoms which are different from those shown by a sensitive rabbit or a sensitive human being. Furthermore, the symptoms of hypersensitiveness are not caused by the liberation of a toxic product, and they are different from the symptoms elicited by exposure of a normal nonsensitive animal to the same antigen. Thus, an allergic individual (if sensitive) responds with characteristic symptoms when exposed to such substances as aspirin or pollen or certain foods. An anaphylactically sensitive animal responds with characteristic symptoms if exposed to egg white or other proteins. These symptoms are entirely different from those which aspirin, pollen, foods, or egg white elicit in nonallergic, nonsensitive, or normal individuals and animals.

When the phenomenon of sensitivity appears in lower animals, it is referred to as anaphylaxis, meaning "without protection." It is employed to denote a state of sensitivity in a lower animal due to exposure to a specific substance and manifested by a characteristic train of symptoms. It is produced at will in the laboratory. When sensitivity appears in the human it is referred to as allergy, meaning, literally, a "changed or altered reaction." The subject of hypersensitiveness, therefore, is divided into two parts: Anaphylaxis (hypersensitiveness in lower animals), and allergy (hypersensitiveness in the human). As will be seen later, there are didactic grounds for this division, in spite of the fact that a strong similarity exists between the two phenomena.

The allergic state may be acquired or induced, or it may be associated with a strong hereditary factor, in which case it is referred to as familial allergy, or atopy, meaning, literally, a "strange disease" (Coca).

A less frequently used term, synonymous with hypersensitiveness, is the word idiosyncrasy. The term intolerance is used interchangeably with hyperergy, and is employed to denote an exaggerated physiologic response to a normal dose of a given substance, usually a drug Thus, if an individual develops signs and symptoms of salicylism (tinnitus, deafness) following the administration of only 5 gr. of aspirin, he is said to show an intolerance or hyperergy to the drug This reaction is quantitative and differs from the allergic reaction to aspirin, which is qualitative. The patient who is allergic to aspirin will show symptoms of asthma, urticaria, or dermatitis—symptoms which are entirely different from those of the toxic effect of the drug. In allergy the symptoms are always the same, regardless of the drug which produces them. Asthma results in the allergic patient from either aspirin or quinine Anergy means the absence of allergy

IMMUNE BODIES IN HYPERSENSITIVENESS

A word is necessary about the terminology employed to designate the immune substances found in hypersensitiveness The immune bodies in anaphylaxis are the antigen, also called anaphylactogen (which is the sensitizing or exciting agent), and the antibody referred to as *anaphylactin* or anaphylactic antibody, which results from antigenic *stimulation* In allergy the substance to which an individual is sensitive is generally called the **allergen.** In that form of allergy which is familial or atopic, the allergen is referred to as atopen. Its corresponding antibody, with which it unites to produce symptoms, is the **reagin.** As will be pointed out later, reagins differ in many respects from other antibodies and, for this reason, the retention of this term is probably justified. They are not present in nonfamilial allergy

CLASSIFICATION

A. Anaphylaxis: the specific sensitivity of lower animals.
B. Allergy: the specific sensitivity of human beings.
   1. Familial (atopic).
   2. Nonfamilial (induced or acquired).

HISTORY

Since there is such a close similarity between the subjects of anaphylaxis and allergy, the history of the development of both will be considered at the same time.

Reference is made by Hippocrates to the existence of an intolerance to certain foods with the development of urticaria and gastric manifestations. This is probably the earliest recognition on record of the hypersensitive state. In the second century A D Galen reports on the development of nasal symptoms from exposure to roses. Van Helmont, about a hundred years later, speaks of the seasonal occurrence of asthma, probably related to exposure to certain vegetation and flowers.

John Bostock, in 1819, described his own paroxysmal, seasonal symptoms referable to the eyes, nose, and chest, which he thought to be due to certain physical agents such as heat and light, as well as to other particles which reach these organs through inhalation. He applied the term "hay fever" to designate this condition which he recognized in himself and in a series of his patients Salter, in 1860, was the first to perform a skin test on himself. He was sensitive to cat hair, and he developed a marked local urticarial reaction upon allowing himself to be scratched by a cat. Upon touching his eyes with his fingers after handling a cat he developed an ophthalmic reaction which he later reported. The earliest exposition on the subject of hay fever, with the observation that it might be due to sensitivity to

pollen, was published by Charles H. Blackley in 1873. This included ophthalmic, nasal, and scratch tests.

The first recorded instance of what must have been anaphylaxis in animals was reported by Magendie in 1839, who discovered that death ensued after a repetition of the injection of egg white in rabbits that had already previously been injected with that substance.

In 1890, Koch reported that tuberculous animals became hypersensitive to normally nontoxic doses of tuberculin. He thus developed the subject of bacterial allergy and the tuberculin test.

In 1894, while he was experimenting with diphtheria antitoxin, Flexner noted that guinea pigs previously treated with dog serum died after a second dose of the same substance.

In 1898, Richet found that dogs would become hypersensitive to eel serum. A few years later, in 1902, Richet concluded that one inoculation of a given protein tends to render an animal hypersensitive to that protein, and, on the basis of this observation, he coined the term "anaphylaxis."

Arthus, in 1903, observed that rabbits inoculated subcutaneously for the second time with the same serum develop a local area of inflammation and necrosis at the point of injection. This resulted from previously established hypersensitiveness.

Von Pirquet, in 1906, employed the term "allergy" to denote a similar kind of sensitivity in human beings.

Since 1910, a great deal of work has been done in the field of allergy, notably by Smith, Rosenau, Otto, Opie, Weil, Besredka, Manwaring, Lewis, Landsteiner, Gay, Doerr, Wells, Walzer, Auer, Tuft, Rackemann, Rowe, Zinsser, Alexander, Coca, Cooke, Cohen, Spain, Vaughan, and many others. In 1922, Coca coined the word "atopy" to indicate the familial or hereditary manifestations occurring in the human.

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B. Allergy: the specific sensitivity of human beings.
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2

Anaphylaxis

DEFINITION
ACTIVE SENSITIZATION
IMMUNE SUBSTANCES
SHOCK ORGAN
TECHNIC OF PRODUCTION OF ANAPHYLACTIC SHOCK BY ACTIVE SENSITIZATION
PASSIVE SENSITIZATION
SITE OF INTERACTION BETWEEN ANTIGEN AND ANTIBODY
DEMONSTRATION OF SPECIFICITY OF ANAPHYLACTIC SENSITIVITY
ROLE OF HEREDITY
PROOF OF PRESENCE OF ANAPHYLACTIC SENSITIVITY
DESENSITIZATION
MECHANISM OF ANAPHYLAXIS AND ALLERGY
SUMMARY

DEFINITION

Anaphylaxis may be defined as a state of hypersensitiveness produced experimentally in lower animals by exposing them for a second time to the same protein This state manifests itself by a group of symptoms known as anaphylactic shock. This is characteristic for each species and is usually fatal. The reaction is the result of a specific antigen-antibody union.

ACTIVE SENSITIZATION

Definition. In response to injection with an antigen such as egg white, a normal guinea pig will develop, in its blood and tissues, specific antibodies against egg white. These are called anaphylactic antibodies. If the animal, some time later, again be injected with egg white, the union between

2

Anaphylaxis

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SUMMARY

Hypersensitiveness is an inclusive term denoting specific sensitivity in animals and human beings to substances harmless to other members of the species. It is a term used interchangeably with **sensitivity**. It includes the phenomenon of **anaphylaxis** (specific sensitivity in lower animals) and **allergy** (specific sensitivity in human beings). The term **intolerance** is used interchangeably with **hyperergy** and is employed to denote an exaggerated physiologic response to a normal dose of a given substance, usually a drug. Another term used synonymously with hypersensitiveness is the word **idiosyncrasy**. **Anergy** means the absence of allergy.

The immune bodies in anaphylaxis are the **antigen**, called the **anaphylactogen**, and the **anaphylactin** or **anaphylactic antibody**. *In allergy the antigen is referred to* as **allergen** or **atopen**. Its corresponding antibody is the **reagin**.

The history of hypersensitiveness dates back to the time of Hippocrates.

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Incubation Period. Following administration for the first time of a given antigen to an animal, a certain period of time must elapse before a second dose of the same antigen will bring about anaphylactic shock. To this lapse of time the term "incubation period" is given It is the time necessary to allow not only for the formation of antibodies (as a result of antigenic stimulation), but for these antibodies to attach themselves to the cells of the shock tissue. This incubation period varies with the species as well as with the amount of antigen injected. If more than one antigen is administered for the first time, the animal will become sensitive to each antigen but the incubation period is not affected The incubation period is for from 8 to 10 days in guinea pigs, and for from 10 to 28 days in rabbits It is longer if the initial dose of antigen is minute.

IMMUNE SUBSTANCES

Nature of Antigen The antigen is the exciting agent in anaphylaxis It is generally agreed that the antigen is a protein. Anaphylactic sensitivity can be produced to nonantigenic substances such as chemicals provided they are previously combined with a protein. Carbohydrates, lipoids, and other nonprotein substances cannot induce anaphylactic sensitization Some proteins are better antigens than others For example, foreign sera and egg white are better antigens than pollens It has also been shown that bacterial proteins have a component capable of inducing anaphylactic sensitivity Furthermore, the secretory products of certain bacteria (for example, tuberculin) may also act as anaphylactogens Bacterial toxins such as diphtheria toxin may be antigenic The antigenicity of a protein depends to some extent on its solubility Since heat has a tendency to coagulate certain proteins, it reduces their solubility and in some instances also their antigenicity. Noncoagulable antigens like ovomucoid are unaffected by boiling as far as

the injected egg white and the anti-egg-white antibodies (anaphylactic antibodies) will give rise to a group of signs and symptoms referred to as anaphylactic shock. The animal is said to have been actively sensitized to egg white.

Route of Production. Animals may be exposed to a given antigen in any one of a number of different ways. Exposure may be brought about intravenously, intraspinally, subcutaneously, intraperitoneally, or intramuscularly. It has been demonstrated that such exposure may also be made by inhalation or by instillation into the conjunctiva.

Amount of Antigen Needed. The amount of antigen necessary to produce anaphylactic sensitivity depends to a large extent on the nature of the antigen, and to some degree on the route of introduction into the body

Specific Differences. Some species of animals are easier to sensitize than are others. Of all species, guinea pigs are the easiest to render sensitive, and the intravenous route of administration is probably the best. Next in order come rabbits, a little more difficult to sensitize than are guinea pigs. Sensitization has been brought about in almost every other species of animal, with varying degree of success.

Prenatal Sensitization. There is some evidence to indicate that it is possible to produce active sensitization of the offspring in utero by injecting the mother with the antigen. After an incubation period it is found that the offspring becomes sensitive to the same antigen. This is an example of active sensitization, inasmuch as it would appear that the antigen has passed through the placenta into the offspring.

Duration. The duration of active sensitization differs with the species. Actively sensitized guinea pigs may retain their sensitivity for from six months to a year, while rabbits or dogs retain it for only a short period of time—about two or three weeks.

Incubation Period. Following administration for the first time of a given antigen to an animal, a certain period of time must elapse before a second dose of the same antigen will bring about anaphylactic shock. To this lapse of time the term "incubation period" is given. It is the time necessary to allow not only for the formation of antibodies (as a result of antigenic stimulation), but for these antibodies to attach themselves to the cells of the shock tissue. This incubation period varies with the species as well as with the amount of antigen injected. If more than one antigen is administered for the first time, the animal will become sensitive to each antigen but the incubation period is not affected. The incubation period is for from 8 to 10 days in guinea pigs, and for from 10 to 28 days in rabbits. It is longer if the initial dose of antigen is minute.

IMMUNE SUBSTANCES

Nature of Antigen. The antigen is the exciting agent in anaphylaxis It is generally agreed that the antigen is a protein. Anaphylactic sensitivity can be produced to nonantigenic substances such as chemicals provided they are previously combined with a protein. Carbohydrates, lipoids, and other nonprotein substances cannot induce anaphylactic sensitization. Some proteins are better antigens than others. For example, foreign sera and egg white are better antigens than pollens It has also been shown that bacterial proteins have a component capable of inducing anaphylactic sensitivity. Furthermore, the secretory products of certain bacteria (for example, tuberculin) may also act as anaphylactogens. Bacterial toxins such as diphtheria toxin may be antigenic. The antigenicity of a protein depends to some extent on its solubility Since heat has a tendency to coagulate certain proteins, it reduces their solubility and in some instances also their antigenicity. Noncoagulable antigens like ovomucoid are unaffected by boiling as far as

the injected egg white and the anti-egg-white antibodies (anaphylactic antibodies) will give rise to a group of signs and symptoms referred to as anaphylactic shock. The animal is said to have been actively sensitized to egg white.

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7. They are not capable of sensitizing the human skin, although there are some experiments which tend to show that in occasional isolated instances it has been possible to sensitize the human skin with a rabbit antiserum. This, however, is the exception rather than the rule.

8 They are neutralized in vitro by the related antigen.

9 They are thermostable.

It is very probable that globulin contains the antibody. It is thought that globulin is perhaps formed in the reticulo-endothelial system. Blocking of the reticulo-endothelial cells with India ink results in a reduction in anaphylactic antibodies and a diminution in the resulting anaphylactic reaction The endothelial cells of the capillaries also may play some role in the anaphylactic reaction just as they play a rather important part in allergy.

Precipitins. Precipitins which develop in the serum of animals rendered anaphylactically sensitive usually parallel the anaphylactic antibodies present. It is hardly likely that these two immune substances are identical. They are found together so constantly that the amount of *precipitins* is usually employed as a gauge or titer for determining the amount of anaphylactic antibodies. In some instances, however, a serum may have a high degree of sensitizing power and yet its precipitin titer is low.

TECHNIC OF "RING METHOD"

This method of testing for the presence and amount of precipitins is described by Tuft "Deposit one drop of immune serum by means of a capillary pipet at the bottom of a series of six small 'ring' tubes These may be made from pyrex glass tubing of 8 to 9 mm. outside diameter. Using a finely calibered capillary pipet, carefully layer a drop of the antigen dilution above the drop of immune serum so as to provide a ring contact. The dilution of the antigen employed will depend upon whether the titer is known If it is, the dilutions should be within this range If unknown,

their antigenicity is concerned. It may be that this is the reason why allergic individuals sensitive to milk or eggs occasionally may drink boiled milk or eat boiled eggs without showing untoward manifestations.

An antigen disappears from the blood of an animal immediately following the appearance of anaphylactic antibodies.

Forssman antigen (heterophile antigen) is an antigen found in the organs of certain animals (guinea pigs, horses, and dogs). Upon injection into rabbits, this antigen has the property of stimulating the formation of hemolysins against sheep cells.

Sensitizing Dose. The initial or primary dose of antigen is referred to as the sensitizing dose.

Exciting or Shock Dose. The second dose, or the dose which produces anaphylactic reaction, is referred to as the exciting or shock dose. The most effective way of producing anaphylactic shock is by injecting the antigen intravenously. The shock dose is usually five to ten times that of the original sensitizing dose. Anaphylactic sensitivity, therefore, may be demonstrated by this method.

Nature of Anaphylactic Antibody. Anaphylactic antibodies are the immune substances resulting from antigenic stimulation and produce symptoms only when combining with the specifically related antigen on or in the cells of the shock organ. By themselves they are nonirritating and nontoxic. These antibodies have the following characteristics:

1. They can sensitize the guinea-pig uterus.
2. They may be transferred to a normal animal and cause it to become passively sensitized.
3. They are specific for the related antigen
4. They are neutralizable in the guinea-pig uterine strip.
5. They are comparatively short-lived (a few weeks)
6. They are associated usually with precipitin formation.

7. They are not capable of sensitizing the human skin, although there are some experiments which tend to show that in occasional isolated instances it has been possible to sensitize the human skin with a rabbit antiserum. This, however, is the exception rather than the rule.

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SHOCK ORGAN

The reaction between an antigen and an anaphylactic antibody takes place in or on the cells of a shock tissue or organ. The shock tissue differs with each species.

In Guinea Pigs. The shock tissue in the guinea pig is the smooth muscle of the bronchi and bronchioles. Union between antigen and antibody in the guinea pig is in the cells of the smooth muscle of the bronchi and bronchioles. This union produces a reaction which results in spasm of the bronchi and bronchioles, so that the animal finds it impossible to expel air from the lungs. This interferes with breathing and leads to asphyxia and death. At autopsy, the lungs are found to be distended (emphysema), and heart block may be observed if the examination is made immediately following the animal's death. A local tissue anaphylactic reaction consisting of localized edema may occur in a guinea pig at the site of the subcutaneous injection of an antigen to which the animal has been sensitized. The exact mechanism of this reaction is not known, although it is supposed to be in the nature of an inflammation brought about as a result of the irritation produced by antigen-antibody combination.

In Rabbits. The shock tissue in the rabbit is the media of the arterioles. If the antigen is given intravenously in the marginal vein of the ear, the first arterioles to be af-

* Tuft, Louis: Clinical Allergy, Philadelphia, W. B. Saunders Co., 1937.

fected are the pulmonary. The antigen unites with the antibody within the muscle cells of the media of these arterioles, producing an irritation which results in spasm and therefore in a constriction at that point This offers an obstruction, so that the right ventricle cannot force the blood through the lungs. Dilation of the right heart follows with subsequent right heart failure, blood is dammed back into the liver; ascites and anasarca result. Autopsy (see Fig 1) shows a marked congestion of the liver and other organs of the body. The animal dies of congestive heart failure with the head retracted and the eyes in a state of exophthalmus. If, however, the antigen is injected subcutaneously in a sensitive rabbit, constriction of the subcutaneous arterioles will result. This leads to cutting off of the local blood supply, and therefore to local necrosis. The resulting condition is referred to as the Arthus phenomenon.

In Dogs. In the dog, the shock organ is the liver. The blood obtained from the vein of a dog in anaphylactic shock is incoagulable. There develops congestion of the liver with stasis in the portal tributaries This is due to contraction of the hepatic vein. Anaphylactic shock cannot be produced in the dog if the circulation through the liver is shunted by performing an Eck fistula. This is done by ligating the portal vein so that it cannot empty into the liver, and by connecting this vein with the inferior vena cava and clamping the hepatic artery. The experiment proves the important role of the liver in the production of anaphylactic shock in the dog

In Cats Some animals, as for example the cat, while unable to be actively sensitized, may be passively sensitized. This inability to sensitize an animal actively may be due to the fact that the animal does not produce sufficient antibodies Anaphylaxis in cats is characterized by a drop in blood pressure, a marked slowing of the heart rate, progressive lowering of body temperature, spasm of the intes-

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FIG. 1. Autopsy findings in rabbit following fatal anaphylactic shock. Note engorged and enlarged liver, dilated heart, and collapsed lungs. Shock dose injected into marginal vein of ear.

tinal smooth muscle, and constriction of the renal blood vessels, but no prolongation of clotting time such as is observed in the dog.

In Other Animals Anaphylaxis has been demonstrated also in rats, frogs, turtles, and chickens. There is some question as to whether true anaphylactic shock has ever been demonstrated in monkeys. So far as we know there is no definite evidence of anaphylactic shock based on an anaphylactic antigen-antibody reaction demonstrated in the human.

There is no evidence to indicate that it is possible to artificially sensitize human beings regardless of whether they are normal or atopic. Numerous experiments have been carried out by various workers and practically all of these experiments have resulted in failure.

It is true that some substances—such as, for example, *horse* serum—if injected at periodic intervals may bring about the presence of skin sensitivity to horse serum and the development of atopic reagins But clinical sensitivity to horse serum under these circumstances is comparatively rare.

The reason for the difference in shock organs in various species must be due to a variation in anatomic development and physiologic response in these animals.

TECHNIC OF PRODUCTION OF ANAPHYLACTIC SHOCK BY ACTIVE SENSITIZATION

Guinea Pig. From one-twentieth to one-tenth of a cubic centimeter of egg white is obtained under sterile precautions This sensitizing dose is injected into a normal 300-Gm. guinea pig subcutaneously or intraperitoneally. Three weeks later the same or a slightly larger quantity of egg white (0 1-0 5 cc.) is injected intravenously into the animal. This injection may be made directly into the heart or into the jugular vein. Shortly after the intravenous injection the

Antiserum. In passive sensitization the serum which is transferred is referred to as antiserum.

Homologous and Heterologous Antiserum. A homologous serum is one which belongs to the same species If one brings about passive sensitization by transferring guinea-pig serum to rabbits, then the transferred serum in such a case is referred to as heterologous serum. Passive sensitization may be brought about with serum of one species transferred to another species, but this does not always hold true, thus, mammalian antibodies do not sensitize birds, and vice versa.

Duration. The duration of passive sensitization is shorter than that of active sensitization. The reason for this may lie in the fact that foreign antibodies are more easily destroyed than the natural antibodies produced by the animal as a result of active sensitization Rabbits produce as a result of active sensitization a high titer serum—that is, a serum rich in anaphylactic antibodies. Since guinea pigs are passively sensitized with comparative ease, the best method of producing anaphylaxis consists in actively sensitizing rabbits and then using the highest obtainable titer rabbit serum (immune serum) for transfer to normal guinea pigs Following passive sensitization the animal may remain sensitive for a variable period of time. This *period is not* the same in all species Guinea pigs remain sensitive for about one or two months if injected with a homologous antiserum, and for a much shorter time (only a few days) [illegible] than one or two days).

Latent Period. As in active sensitization, a period of time must elapse following the injection of a normal guinea pig with the serum of a sensitive guinea pig or rabbit (anaphylactic antibody-containing serum) before anaphylactic sensitivity is established This period is usually four to six

animal usually shows the characteristic symptoms of anaphylactic shack.

Rabbit. HORSE SERUM. Coca advises the following technic: "Inject 0 2 cc. to 1 cc. of horse serum subcutaneously into a rabbit. This dose is repeated in five days, and then again in eight days. From then on 0.2 cc. of horse serum is given every other day for seven injections. Anaphylactic shock is produced by the injection of 2 cc. of horse serum intravenously in the marginal vein of the ear five days after the last injection." *

EGG WHITE (Grove *). First day, 0.5 cc. intravenously; sixth and eleventh days, 2.0 cc intraperitoneally; daily from the twelfth to the nineteenth days, inclusive, 1 0 cc. intraperitoneally, twenty-sixth day, 4.0 cc. subcutaneously; thirty-third to thirty-sixth days, test by intravenous injection of 2.5 to 4.0 cc.

CHICKEN CORPUSCLES. Grove found that active sensitization in the rabbit is invariably accomplished by a primary intravenous injection of 2.0 cc. of washed chicken corpuscles followed in six days by the subcutaneous injection of 3.0 cc of the same antigen.

PASSIVE SENSITIZATION

Definition. It is also possible to sensitize an animal by injecting it with the antibody-containing serum (**antiserum**) of a sensitive animal. A given quantity of the serum of an actively sensitized guinea pig or rabbit is injected intravenously into a normal guinea pig As a result of this procedure the animal receiving the injection becomes anaphylactically sensitive, so that upon being subsequently injected with the related antigen it will develop anaphylactic shock. This method of producing sensitivity is called **passive sensitization.**

* *Coca*, A. F., M. Walzer, and A A Thommen Asthma and Hay Fever, Springfield, Ill., Charles C Thomas, Publisher, 1931

Incubation Period of Active Sensitization. This period is necessary for the formation and attachment of anaphylactic antibodies to the shock tissue.

Latent Period of Passive Sensitization. The necessity of a latent period in passive sensitization is similarly proof of the cellular rather than the humoral site for the interaction between antigen and antibody.

Neutralization. If one injects a mixture of antigen and its specific antibody intravenously into a normal guinea pig, anaphylactic shock does not occur. It is therefore apparent that antigen can neutralize its corresponding anaphylactic antibody in the circulation

Perfusion Experiments. These prove that the site of interaction between antigen and antibody must be in the shock tissue After replacing over 90 per cent of the blood of a sensitive guinea pig by perfusion with normal blood, the animal is still sensitive. In other words, one can demonstrate anaphylactic shock in these guinea pigs because antibodies are still attached to the shock tissue.

The Uterine Strip Reaction of Dale-Schultz. This is a *positive* proof of the cellular theory because a strip of uterine muscle removed from a sensitive animal and suspended in a Dale bath will always react upon the addition of the specific antigen The sensitized tissue cells react in this manner when removed from the body

DEMONSTRATION OF SPECIFICITY OF ANAPHYLACTIC SENSITIVITY

If a normal guinea pig is actively sensitized with horse serum and egg white administered at the same time, and 24 hours later a sublethal dose of horse serum is injected, the animal will lose its sensitivity to horse serum. However, if within a few hours or a day the animal receives 0.3 cc. of egg white intravenously, anaphylactic shock will still result. This demonstrates the specificity of anaphylactic sensi-

hours, and is called the latent period. It represents the time required for the antibodies thus transferred to attach themselves to the shock tissue. If the shock dose is injected before *the six-hour interval, anaphylactic shock does not* occur. In other words, if the union between antigen and antibody occurs in the circulation, the antigen neutralizes the antibody and no symptoms occur. If, however, time is allowed for these antibodies to attach themselves to the sensitive tissue, the antigen upon injection into the guinea pig will reach and combine with the antibodies on or in the shock tissue. This union will irritate the cells and produce anaphylactic shock.

Technic of Production of Passive Sensitization. Five to 10 cc. of the serum of an actively sensitized guinea pig (sensitive to egg white) is injected into a normal guinea pig intravenously. Twenty-four hours later, one-twentieth of a cubic centimeter of egg white is given intravenously. Anaphylactic shock will result.

Since it is easier to sensitize guinea pigs passively with rabbit antiserum, *the following technic may be employed:* Inject 2 to 3 cc of a high titer rabbit antiserum (egg white or horse serum) intraperitoneally into a normal guinea pig. The intravenous injection of 1 cc. of egg white or horse serum 24 hours later will produce anaphylactic shock in the guinea pig.

Both active and passive sensitization may take place in lower animals in utero, for both antigen and antibody can pass through the placenta.

SITE OF INTERACTION BETWEEN ANTIGEN AND ANTIBODY

The site of interaction between antigen and antibody must be in the cells of the sensitive (shock) tissue, and not in the circulation. In favor of this view one can cite the following as proof:

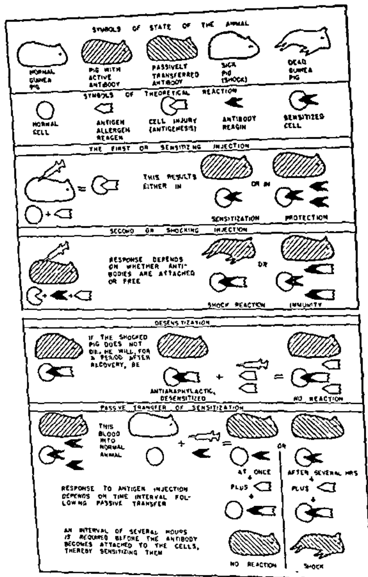


Fig. 2. Schematic [illegible]

ac

an

[illegible]

tivity. The same experiment may be repeated in a Dale bath with the uterine strip sensitized to two antigens.

ROLE OF HEREDITY

Heredity plays no role in the transmission of hypersensitiveness in lower animals but represents merely a passive sensitization of the young by the maternal antibodies that have passed through the placenta. On crossing sensitized female guinea pigs with normal male guinea pigs, the offspring may be anaphylactically sensitive If they are, their sensitiveness *will be found to be the same as that of the* mother In other words, this type of sensitivity is congenital and represents passive sensitization. Sensitivity is always due to the same antigen as that used in sensitizing the mother.

PROOF OF PRESENCE OF ANAPHYLACTIC SENSITIVITY

In order to prove that a given animal is anaphylactically sensitive to a protein *the following* tests may be made

1. Test the serum for precipitins (by the contact test)
2. Attempt passive sensitization with the animal's serum.
3. Perform the Dale-Schultz test for sensitivity of suspended uterine strip.
4. Attempt to induce anaphylactic shock.

DESENSITIZATION

Definition. If a sensitive guinea pig is injected with a sublethal dose of antigen subcutaneously, it will be found that complete loss of sensitiveness may result. This is due to the fact that the slowly absorbed antigen gradually neutralizes the antibodies attached to the shock tissue. This procedure is referred to as *complete desensitization.*

Partial Desensitization. Depending on the technic, time, and quantity of antigen injected, the resulting desensitiza-

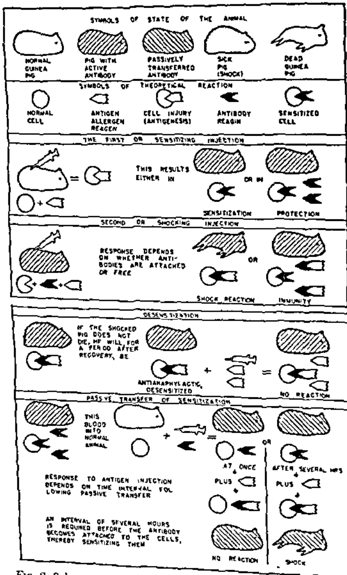


Fig 2 Schematic representation of phenomena of anaphylaxis; activ... a... . (Courtesy, Topley ... and Immunology,

tion may be partial or complete. When desensitization is partial, slight symptoms may result from subsequent injections.

Complete Desensitization. In complete desensitization the animal becomes to all intents and purposes nonsensitive or normal, so that anaphylactic shock will not result from the further injection of the same protein. Complete desensitization, therefore, is possible in anaphylaxis.

Nonspecific and Partial Desensitization. This may also be brought about by the administration of a substance other than the specific antigen, for example, peptone, foreign serum, inorganic salts, etc. Sensitive animals may become partially desensitized by nonspecific agents, so that anaphylactic shock may be brought about only by the injection of a considerably larger amount of the antigen. This interference with anaphylactic shock is referred to as nonspecific partial desensitization. It is comparable with similar results obtained in the human by the administration of nonspecific agents such as calcium, peptone, etc

Antisensitization. Another form of interference with sensitization consists in injecting a guinea pig with a large dose of a nonspecific foreign serum, such as dog serum, either at the same time or shortly before the animal receives a sensitizing dose of the antigen. Under these circumstances it is found that active sensitization occurs either not at all or to a lesser degree than in a group of control animals. In this manner it is possible to interfere with the formation of anaphylactic antibodies and therefore with the development of anaphylactic sensitivity The same result may be brought about by nonspecific means, such as by blocking of the reticulo-endothelial system or by starvation and *infection. This form of interference with the development of sensitization is referred to as antisensitization*

Masked Anaphylaxis. *Still another form of interference with anaphylaxis is referred to as masked anaphylaxis. In*

this case, the guinea pig is given a second dose of the specific antigen during the incubation period. As a result of this administration, it is found that anaphylactic shock does not occur if the usual shock dose of antigen is administered at the end of the incubation period; but if a sufficiently large dose of antigen is given symptoms may result. It is a form of interference with the development of anaphylaxis, and is due to the fact that the antigen injected before the animal has actually become sensitive has caused an increased production of antibodies in the circulation; so that, on subsequent administration of the usual shock dose of antigen, most of it is already taken up or neutralized by the circulating antibodies. Very little of the antigen is left to reach the antibodies attached to the cells of the shock tissue If, however, a sufficient multiple of this dose is given, part of the antigen will be neutralized by the circulating antibodies, and the rest may reach the antibodies attached to the cells of the shock tissue and produce symptoms of anaphylaxis. These symptoms, however, are slight because only a few of the antibodies have had a chance to become attached to the cells of the shock tissue.

Technic of Desensitization. ANTISENSITIZATION. Inject a guinea pig with 5 cc. of dog serum or peptone subcutaneously at the same time or shortly before giving the sensitizing dose of egg white Active sensitization to egg white in this animal either does not occur or else will occur to a lesser degree than in control animals which receive an injection of egg white only This phenomenon is referred to as antisensitization.

COMPLETE DESENSITIZATION. Antisensitization is brought about in a normal guinea pig by the technic described above. However, if, instead of injecting the normal shock dose of horse serum (0 1 to 0 5 cc.) intravenously on the fifteenth day, one injects two or three small doses (0.05 cc. or less) of the antigen (horse serum) subcutaneously, the

animal will be completely desensitized and will show few if any symptoms of shock, behaving subsequently like a nonsensitive, normal guinea pig.

MECHANISM OF ANAPHYLAXIS AND ALLERGY

Lewis' Histamine Theory. There are many theories which attempt to explain the phenomenon of anaphylaxis and allergy. Of these, the most recent is that advanced by Sir Thomas Lewis. This assumes that the union of antigen and antibody in the shock tissue causes an irritation in or on the cells of the tissue, with the resulting liberation of a histamine-like substance which produces the physiologic effect characteristic of anaphylaxis or allergy. In all likelihood this change is chemical. That histamine is a normal component of many tissues can be demonstrated easily. Likewise, it would seem that many of the manifestations characteristic of anaphylactic shock, such as contraction of smooth muscle and of the uterine horn, and the drop in blood pressure, can be duplicated by the administration of histamine. The injection of histamine produces shock in guinea pigs, rabbits, and other animals which is in many ways indistinguishable from anaphylactic shock (anaphylactoid reaction).

Lewis' work on the urticarial wheal would indeed explain the mechanism of allergy on the same basis. If we accept this theory—and it is the most plausible one thus far advanced—we must do so, however, with the understanding that several objections which have so far been offered have not as yet been fully answered.

Objections to Histamine Theory. One of the objections raised deals with a phenomenon best observed in the Dale-Schultz experiment on anaphylaxis. The Dale-Schultz technic consists in suspending a strip of virgin guinea-pig uterine muscle in a bath of Ringer's solution. If the muscle strip is from a guinea pig sensitive to egg white,

one will find that, upon adding a small quantity of egg white to the bath, the smooth muscle strip will contract. Given a strip of muscle from a guinea pig sensitive to two antigens—let us say egg white and horse serum—the strip will contract to a certain extent following the addition of a small quantity of egg white. The second dose of egg white elicits a smaller contraction, with each subsequent addition of egg white the contraction becomes less until no contraction is obtained, because all the anti-egg-white antibodies are exhausted or neutralized by the antigen. At this time the addition of horse serum, however, will elicit a strong contraction Those who object to the histamine theory ask why the supply of histamine is not completely exhausted by the series of additions of the first antigen (egg white). A possible answer to this objection is that following the successive additions of egg white the antibody is exhausted, but some histamine is still left to be liberated by treatment with horse serum

Another objection is that offered with respect to the *role* played by the supposed liberation of histamine or a histamine-like substance in allergic conditions in man. The question is asked why should the liberation of this same substance produce hay fever or asthma *in one* patient and eczema or urticaria in another?

Still another objection offered is the inability of histamine to produce a decrease *in* or loss of blood coagulability similar to that produced by anaphylactic shock, and the failure of histamine to desensitize animals

Anaphylactoid reactions produced by the injection of histamine are not accompanied by eosinophilia Furthermore, there is no increase in the blood histamine during anaphylactic shock or during an allergic state.

Regardless of these objections, the fact remains that Lewis' theory is the most plausible explanation thus far offered of the phenomena of anaphylaxis and allergy.

In connection with the role of histamine in anaphylaxis and allergy, mention should be made of some recent work concerned with the production of histamine-specific antibodies by the injection into guinea pigs of histamine as a specific hapten conjugated with an inert protein carrier. By such treatment it is found that animals develop a high titer of antihistamine precipitins, acquiring some immunity against further injection of histamine. Furthermore, it is much more difficult to produce anaphylaxis in these animals (by injection with egg albumen) than in a control series. The application of these results to clinical allergy is as yet not established.

SUMMARY

Anaphylaxis is a state of hypersensitiveness produced experimentally in lower animals by exposing them for a second time to the same protein. Active sensitization is the procedure whereby an animal is rendered anaphylactically sensitive by being exposed to an antigen. This exposure may take place intravenously, intraspinally, subcutaneously, intraperitoneally, or intramuscularly. Active sensitization of the offspring in utero is possible and is brought about by injecting the mother with an antigen just before birth. The duration of active sensitization differs with the species. The incubation period in active sensitization is the period of time which must elapse between the first (sensitizing) and the second (shock) dose of antigen in an animal.

The immune substances in anaphylaxis are the antigen and the anaphylactic antibody. Some proteins are better antigens than others. The initial or primary dose of antigen is referred to as the sensitizing dose. The second dose, or the dose which produces anaphylactic shock, is referred to as the *exciting or shock dose.* The anaphylactic antibodies are the immune substances resulting from antigenic stimulation and produce symptoms only when combined with the specifically related antigen. Precipitins usually parallel

the anaphylactic antibodies. The shock organ is the organ in which the union between antigen and anaphylactic antibody takes place. In the guinea pig it is the smooth muscle of bronchi and bronchioles. In the rabbit it is the media of the arterioles. In the dog it is the liver.

Passive sensitization is the procedure whereby an animal is rendered anaphylactically sensitive by injecting it with the antibody-containing serum (antiserum) of a sensitive animal. A homologous antiserum is one which belongs to the same species. A heterologous antiserum is one which belongs to a different species. The latent period is the period of time which must elapse in passive sensitization between transfer of antiserum to a normal animal and before anaphylactic shock can be produced by the administration of the corresponding antigen.

The site of interaction between antigen and antibody is in the cells of the shock organ This is proved by the presence of: (1) An incubation period of active sensitization; (2) the presence of latent period in passive sensitization; (3) the ability of antigen to neutralize its corresponding anaphylactic antibody in the circulation; (4) perfusion experiments, (5) the Dale-Schultz technic.

Heredity plays no role in anaphylaxis.

The presence of anaphylactic sensitivity may be demonstrated by (1) The presence in the serum of *precipitins;* (2) passive sensitization with the animal's serum; (3) the Dale-Schultz technic, (4) an attempt to induce anaphylactic shock.

Desensitization is the complete loss of sensitiveness which may be brought about by the injection of a suitable quantity of antigen in a sensitive animal It may be partial or it may be complete Partial desensitization may be brought about by *nonspecific* agents. Antisensitization is the term applied to a procedure which brings about an interference with the *formation* of anaphylactic antibodies. Masked anaphylaxis is another form of desensitization. In this case

the animal is given a second dose of the same antigen during the incubation period As a result of this administration it is found that anaphylactic shock does not occur if the usual shock dose of antigen is injected at the end of the incubation period; symptoms may result if a sufficiently large dose of *antigen is given at this time. The mechanism* of anaphylaxis is best explained by the Lewis theory. This is based on the liberation of histamine or a histamine-like substance resulting from the union of antigen and antibody in the cells of the shock tissue.

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3
Allergy

DEFINITION
CLASSIFICATION
ETIOLOGY
PHYSIOLOGY
PATHOLOGY
IMMUNOLOGY
CLINICAL MANIFESTATIONS
COMPARISON WITH ANAPHYLAXIS
SUMMARY

DEFINITION

As indicated before, the term allergy is used to denote the specific hypersensitiveness of human beings It may be (1) familial (atopic) or (2) acquired or induced

CLASSIFICATION

Familial Allergy (Atopy). Hay fever, asthma, eczema, allergic rhinitis, and some cases of urticaria, migraine, and angioneurotic edema

Acquired or Induced (Nonfamilial).

1 Serum allergy (serum sickness, accelerated serum reaction).

2 Drug allergy

3 Contact dermatitis (skin allergy).

4 Allergy to infectants and infestants (bacteria, parasites, fungi)

5 Allergy to physical agents (heat, cold, sunlight, effort).

Some of the manifestations classified under induced allergy, such as certain forms of serum and drug allergy, may also be familial.

ETIOLOGY

Incidence. It is estimated that about 10 per cent of the population show allergic manifestations of the familial type. In addition, about 30 to 40 per cent more show allergic manifestations of the acquired type, or mild unusual reactions to given substances, a form of allergy referred to as minor allergy.

Type of Allergen. The type of allergen involved is of great importance. It has been shown, for example, that it is not possible to sensitize human beings to such common substances as orris root or pollen, substances to which the individual is constantly exposed, on the other hand, it has *been possible to sensitize individuals to horse serum and* other biologic products It would appear that acquired allergy is more likely to develop if the allergen is one which is more or less unusual and strange to the individual, rather than a common substance with which he constantly comes in contact.

Date of Onset. About one-half of those who are frankly allergic date the onset of their allergy to the first decade of life. The stronger the antecedent family history of allergy, the earlier the onset of allergic manifestations.

Effect of Climate and Environment. Climate and environmental factors play an important role in the etiology of allergic conditions, as might well be expected Climatic changes contribute to the development of allergies of the respiratory tract. There is considerable evidence to indicate that fluctuation of barometric pressure, especially a low pressure, *has a definite effect on an individual's sense* of well being. Furthermore, these fluctuations seem to affect most of the body functions and are manifested often as symptoms of disease. This seems to be particularly true with reference to respiratory allergy. Changeable weather, low barometric pressure, fog, and increased humidity always

aggravate the extent and severity of respiratory allergy. Other climatic conditions which determine the amount of pollen in the air are the wind, the amount of dust, the severity of heat or cold, etc. Environmental forces include exposure to dust, fungi, occupational allergens, and botanical flora, all of which may influence the appearance of allergic symptoms. Mechanical and chemical irritants are also etiologically important.

Effect of Heredity. The weight of available evidence points to the fact that in one group of allergic conditions (the familial or atopic group—asthma, hay fever, eczema) heredity plays an important role. It is a germinal type of transmission, through the germ plasm and not through the placenta. The hereditary factor is not due to the transmission of antibodies through the placenta, for these antibodies, otherwise referred to as reagins, are incapable of passing through the placental tissue; furthermore, the offspring is frequently sensitive to a substance other than that to which the mother is sensitive. Frequently the history of sensitivity is on the paternal side. Herein may be seen a definite difference between familial allergy and anaphylaxis On the other hand, occasionally the fetus may be actively sensitized in utero by the passage of antigen (a food ingested by the mother) through the placenta. For example, it has been shown that overindulgence on the part of the mother in certain protein foods may so sensitize the fetus that after birth, on coming in contact with this food presumably for the first time, the child will develop allergic symptoms But this form of transmission is really congenital and not hereditary.

Just what is transmitted by heredity in an allergic person is not entirely clear. We know that an atopic individual inherits the predisposition to manufacture antibodies or reagins against a given substance, provided he has had sufficient and suitable contact with that substance. This

property, however, is not limited to atopic individuals. *Thus it is found that nonallergic people on occasion may* develop reagins upon proper stimulation. Nonallergic individuals who have had or have intestinal parasites may develop reagins to the proteins of these worms.

There are reports in the literature (some by the writer) of instances where the injection of biologic products such as horse serum, pituitrin, insulin, and liver extract produces, both in normal and in atopic persons, skin-sensitizing antibodies identified as reagins. The production of reagins in normal individuals under these circumstances is usually accompanied by the formation of other immune bodies, such as anaphylactic antibodies and precipitins In familial allergic (atopic) patients, such as hay-fever patients, reagins are not accompanied by the presence of anaphylactic antibodies and precipitins Furthermore, in most instances of worm infestation or acquired allergy, reagins thus produced last but a short time. Upon receiving a subsequent injection of insulin or pituitrin, nonallergic persons who have developed reagins as a result of prior administration of insulin or pituitrin may show a reaction, but the reaction is, as a rule, a swelling at the point of injection, or some constitutional symptoms such as malaise and fever. In nonatopic individuals, in those who do not have inherited allergy, the reaction is never that of asthma or hay fever In other words, the reaction is not atopic. The reason for this is the absence of an inherited shock organ (skin and mucous membranes). It would appear, therefore, that in order to have allergic manifestations of the asthma–hay-fever–eczema type it is necessary for the individual to receive by heredity not only the ability to manufacture antibodies (reagins), but also a sensitive shock organ

Patients with allergic manifestations such as asthma, hay fever, and eczema give a positive antecedent family history in 50 per cent or more of the cases. *This is indeed a very*

high percentage when compared with a similar group of nonallergic patients. The argument against the role of heredity as a factor in allergy has been presented by citing some series of allergic patients in which the percentage of antecedent positive history of allergy is very low Failure to obtain an antecedent positive history of allergy, however, does not in itself constitute proof against the role of heredity in these conditions. In many instances, particularly in clinic practice, patients are not sufficiently well informed with respect to the presence of allergy in their antecedents. In other instances the individual is not sufficiently intelligent to understand what is asked of him. In still other instances the antecedents may have had some allergic manifestations (for example, allergic rhinitis or hay fever) and the condition was referred to at a time when little was known about allergy, as "catarrh," or just frequent "colds."

A study undertaken by the writer and involving several sets of allergic twins helps to strengthen the theory of the hereditary transmission of major allergies. Not only do these twins have a positive antecedent family history of allergy, but in most instances the shock organ involved and the clinical manifestations are practically indentical in both members of each set of twins.

Effect of Contact. An individual whose antecedents have had allergic manifestations may, therefore, as a result of some form of exposure such as inhalation of pollen or ingestion of milk develop reagins against these substances. Subsequent exposure to these substances will presumably bring about a union of the allergen with the corresponding reagin; and if the individual inherits also a shock organ (a sensitive nasal or bronchial mucous membrane) this union will supposedly cause the liberation of a histamine-like substance, usually referred to as the H-substance, in the cells of the shock organ, with resulting allergic manifestations

Previous contact is, therefore, essential. This is shown by the well-known experiment of Coca and Grove (quoted by Tuft), in which 36 timothy hay-fever subjects residing in Germany were tested with pollen. Of these, 35 showed a negative reaction to ragweed. Only one gave a positive test to ragweed, and this patient was the only one of the entire group who had visited the United States and therefore had been exposed to ragweed, for ragweed is not found in Germany. In view of the fact that about 50 per cent of all timothy hay-fever patients in the United States give positive reactions to ragweed, one would explain the failure to obtain positive reactions in a similar percentage of timothy hay-fever patients in Berlin as due to the lack of previous contact to ragweed on the part of these patients. It goes without saying that heredity plays no role in the production of those allergic conditions which are designated as acquired.

Occasionally a large section of the population may acquire an allergy by suitable exposure For example, individuals who are not allergic to poison ivy can be rendered allergic by proper and repeated exposure to poison ivy. In a similar way suitable exposure to adequate dosage of biologic products such as insulin, pituitrin, pancreatic extract, and liver extract, sensitize some individuals regardless of whether they are allergic (atopic) or normal. Therefore, it would seem that it is largely a matter of exposure, dosage, and type of allergen.

In a sense, *both the familial and the nonfamilial forms* of allergy are acquired because previous contact is necessary in both. But in one instance the allergy is acquired by a natural method of exposure, while in the other (the nonatopic) it develops through unnatural methods; i.e., the administration of serum by injection.

Another form of sensitization in the human where previous contact plays a role is by blood transfusions This

may take one of two forms In the first, the sensitization reaction is severe and characterized by fever and a hemolytic reaction, following the second transfusion of an Rh-negative patient with Rh-positive blood As a result of the first transfusion the recipient develops immune anti-Rh isoantibodies which play a role in bringing about the reaction following the second transfusion. The second form of allergy by blood transfusion is that of a nonallergic recipient who receives blood from an allergic donor. Upon ingestion of food to which the donor is sensitive, and against which the donor may have circulating reagins, the patient develops an attack of asthma or urticaria Similarly, the recipient may be an allergic individual. As a result of blood or plasma transfusion he may receive some protein to which he is sensitive and develop allergic manifestations.

Causes of Allergy: Exogenous Allergens

Inhalants These allergens reach the body through absorption from the mucous membrane of the nose and the respiratory tract. They include pollen, animal danders (such as horse dander, feathers, rabbit hair, cat hair, dog hair), orris root, insecticide, house dust, cottonseed, occupational dusts, etc Most of these allergens will be discussed in a subsequent chapter.

Sensitivity to human dander must also be considered under the heading of inhalants because it has recently been shown that allergic infants and children may be sensitive to the dander of their mother, especially if the mothers have seborrheic dermatitis.

There are many references in the literature to allergy to insects and their emanations. These include such manifestations as bronchial asthma, urticaria, and allergic rhinitis resulting from the inhalation of emanations from such insects as household ticks, the caddis fly, moths, butterflies, locusts, honey bees, yellow jackets, and May flies It is important to keep this possibility in mind, especially in the

case of allergic patients who live near bodies of water. In many of the reported cases, positive intradermal reactions are obtained to extracts of these emanations, and in some instances desirable therapeutic effects result from proper "desensitization" treatment.

Ingestants (Foods). Among these the most common are *milk, eggs, and cereals. Next in order are fish, nuts, spices,* vegetables, and fruits. Important among vegetables are celery, string beans, and lima beans; important among fruits are bananas, oranges, strawberries, and lemons. The incidence of food allergy is probably greater than we realize. Careful history taking reveals that many individuals who are not otherwise allergic have an intolerance to or dislike for certain foods. Following the ingestion of many foods these individuals experience certain bodily as well as gastric discomforts. In addition, allergic individuals may develop certain well-known clinical conditions such as bronchial asthma, allergic rhinitis, allergic dermatitis, urticaria, gastro-intestinal symptoms (including abdominal pains, diarrhea, canker sores, and colitis), and symptoms referable to many of the other systems, as the result of ingestion of foods to which they are sensitive In some instances allergy develops as a result of overindulgence in certain types of food. For this reason the most frequent causes of allergy are the common foods.

Food sensitivity has been demonstrated to exist from infancy to old age. Within recent years pediatricians have become increasingly aware of the importance which food allergy plays in the production of symptoms in the infant and growing child.

Some allergens have certain active principles in common. Thus there is a common allergen in cow serum, cow dander, and cow milk. The same thing holds true with respect to chicken feathers and chicken meat, or horse dander, horse

serum, and horse meat. Desensitization to one of these substances may lead to desensitization to the others. It is also likely that common active principles are contained in many of the vegetables, fruits, and nuts.

Allergic manifestations following the ingestion of foods may occur almost instantly or from two to 12 hours after the ingestion of the food. It has been shown by the passive transfer test that many foods are absorbed through the gastro-intestinal tract in an unchanged form There is frequently the possibility, too, of summation of effect; in other words, the individual may be only slightly sensitive to a number of foods and if he ingests those foods in a short period of time there will be a summation of effect resulting in allergic symptoms These symptoms may last over a variable period of time. Their intensity may also be varied depending on the degree of sensitivity as well as on the amount of allergen absorbed. For this reason gastro-intestinal absorption plays an important role It does not necessarily follow that allergic manifestations will occur immediately after the ingestion of a food. In view of this it is not advisable for a patient to partake of a suspected food merely because he has not developed asthma or other symptoms shortly after eating it In many instances it is necessary for the patient to partake of a given food for several days before it will cause any disturbance.

The clinical manifestations of food allergy are varied The fact that the patient knows he is allergic to one food suggests the advisability of studying him for additional sensitivity to other foods

Contactants Contactants include a large group of substances which produce skin allergy by direct physical contact—to mention only a few: cosmetics, including nail polish, face powder, and face and hand lotions (karaya gum), and occupational materials, such as plastics, rubber,

leather, etc. These will be taken up in detail in the chapter dealing with contact dermatitis. Occasionally, especially in infants and children, one may find contact allergy to foods manifesting itself in eczematoid patches around the lips, face, and even on the hands. In other instances individuals may be sensitive to the inhalation of certain foods, such as baking flour and the odor of cooking and fried foods. Instances of allergic eczema and bronchial asthma are known to have been brought about by a sensitivity to the odor of foods. The mother of one little boy states that the child develops a severe attack of asthma if he is exposed to an open can of sardines or if he is in the house when fish is being cooked. Another child develops a severe attack of generalized eczematoid dermatitis when the mother opens an egg in his presence.

Injectants. This group of allergens includes substances, usually drugs and biologicals, which are injected into an individual. Allergic symptoms may develop from the injection of foreign sera (antitetanic serum) due to a sensitivity to horse serum. Allergic manifestations may result from the injection of insulin, pituitrin, liver extract, and other biologic products. Such drugs as salvarsan, the sulfonamides, and penicillin may also act as allergens. Under this heading would come also allergy to insect bites, such as bees, wasps, and bedbugs. There are many reports of severe local and systemic reactions associated with nasal allergy, asthma, and generalized urticaria following bee stings. The allergy seems to be due to the protein of the insect and not to the venom. The author has seen one instance of persistent generalized urticaria in a nurse who had been thought to be sensitive to foods. This girl's condition improved when she went home for a few days. Investigation proved her urticaria to be due to the bites of the bedbugs with which her rooming-house bed was infested.

Physical Agents. Physical agents causing allergy are sunlight, heat, and cold Exposure to these agents may produce urticaria, angioneurotic edema, nasal and respiratory symptoms, or other allergic manifestations.

[illegible]

the tuberculin type of sensitivity as well as the causative association between infection in the paranasal sinuses and bronchial tree on the one hand, and nasal allergy and bronchial asthma on the other. Fungi may produce an allergy not only by inhalation of spores but also as a result of previous skin infection

Parasitic Infestation. This may give rise to an allergy to the proteins of the worm, so that a whealing reaction is obtained by testing the individual with a properly prepared extract of the parasite.

PHYSIOLOGY

A discussion of the physiology of allergy must take into consideration the influence of the autonomic nervous system The autonomic nervous system includes the sympathetic and the parasympathetic (vagus) nervous system The two are definitely antagonistic, and stimulation or the preponderance of one over the other leads to a well-defined train of disturbances

The sympathetic ganglia are located along the vertebral column The nerve fibers are derived from the gray matter of the lumbar and thoracic spinal segments. These ganglia are closely interrelated and send out fibers to distant parts of the body. The whole system acts as a unit. Stimulation or preponderance of the sympathetic nervous system produces tachycardia, dilatation of the bronchi, hyperactivity of the sweat glands, a reduction in the blood clotting time,

leather, etc. These will be taken up in detail in the chapter dealing with contact dermatitis. Occasionally, especially in infants and children, one may find contact allergy to foods manifesting itself in eczematoid patches around the lips, face, and even on the hands. In other instances individuals may be sensitive to the inhalation of certain foods, such as baking flour and the odor of cooking and fried foods. Instances of allergic eczema and bronchial asthma are known to have been brought about by a sensitivity to the odor of foods. The mother of one little boy states that the child develops a severe attack of asthma if he is exposed to an open can of sardines or if he is in the house when fish is being cooked. Another child develops a severe attack of generalized eczematoid dermatitis when the mother opens an egg in his presence.

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PATHOLOGY

There is no typical lesion characteristic of the allergic phenomenon The lesion of urticaria, for example, is different from that of eczema, and that of eczema is different from that of bronchial asthma. Furthermore, some difficulty is encountered in the study of many of these lesions because the primary lesion is usually temporary, so that we deal with a reversible inflammatory reaction. For this reason characteristic morphologic changes are not demonstrable by microscopic examination However, allergic reactions are often accompanied by an eosinophilia in the blood and tissues and in the nasal secretions and sputum. Edema of the mucous membrane and skin (urticarial wheal) is another common finding in allergy. This is probably due to an increased capillary permeability owing to the fact that the endothelium of the vessels is the site of the reaction. Smooth-muscle spasm, particularly spasm of the bronchial musculature, is held by some authorities to be the outstanding pathologic physiology in asthma, but in all likelihood the probability is that both edema and spasm play a role

In the more chronic form of allergic conditions certain more or less permanent changes supervene. In hay fever, for example, there occurs hypertrophy of the nasal mucous membrane with polyp formation followed frequently by infection, in bronchial asthma there develops a hypertrophy of the smooth muscle and mucous glands of the bronchial wall; and the skin of the patient with eczema undergoes thickening and lichenification A description of detailed morphologic changes which accompany the various allergic conditions such as nasal allergy and bronchial asthma will be included in the chapters dealing with these disorders

a rise in blood pressure, dilatation of the pupils, and relaxation of the gastro-intestinal tract (atonic response). These results are referred to as adrenergic. The drugs which act on the sympathetic system are the phenol-amine group: adrenalin, paredrine, propadrine, neosynephrin, ephedrine, and benzedrine (amphetamine sulfate). Of these the effect of adrenalin is short-lived, while the effect of paredrine, propadrine, and neosynephrin is longer. Ephedrine and benzedrine have a marked central effect. Atropine is synergistic with the adrenergic series by reducing acetylcholine (paralyzing the parasympathetic).

The parasympathetic (vagus) nervous system is also widely distributed through the various organs of the body. Ganglia are located close to the organs The influence of the central nervous system on the parasympathetics is much more profound than in the case of the sympathetics. Stimulation of the parasympathetic system leads to a state referred to as vagotonia. There is evidence to show that this state is somewhat associated with that of allergy. Just as the adrenergic effect is similar to that of stimulation of the sympathetic nervous system, just so other substances, either identical with or closely related to acetylcholine, produce manifestations closely similar to those of vagotonia, these manifestations include contraction of the smooth muscle of the intestines, lowering of the blood pressure, and lowering of the pulse rate. This is referred to as a cholinergic effect. It is brought about by the phenyl-amine group of drugs. acetylcholine (effect evanescent), mecholyl (longer duration), and pilocarpine.

It should be stated that in many instances the cleavage of function of each *series of drugs and of each subdivision of* the autonomic nervous system is not very clearly defined and that overlapping of function takes place as may be cited in the case *of sweating.*

local sensitization lasts from a few days to a month. This is referred to as the Prausnitz-Kustner or passive transfer reaction. The technic of this test is as follows: One-tenth of a cubic centimeter of the previously Seitz-filtered and now sterile serum of a patient who is sensitive, let us say, to fish, is injected intradermally into the skin of a normal, nonallergic person. About 6 to 10 hours later, after the reagins have had time to attach themselves to the cells of the skin, a small amount of allergen (fish in this case) is injected into the sensitized site. Shortly thereafter one obtains a positive reaction as evidenced by the formation of a wheal. This positive reaction can be taken as proof that the transferred serum contained anti-fish reagins. It is therefore a technic which can be employed for clinical diagnostic purposes as well as for the purpose of determining the presence of reagins. In performing the test, needless to say, certain precautions must be followed. The Wassermann reaction of the patient should be negative. A control, using an intradermal test with the allergen (in this case fish), is performed on the substitute to make certain that he is not sensitive to fish. Finally, it is well to warn the substitute not to eat the foods to which one suspects the patient might be sensitive, for, as has been demonstrated, sufficient food protein may be absorbed through the gastro-intestinal tract and reach the substitute's skin to give rise to positive re-

[illegible] patients when no uninvolved skin is available.

3 Reagins transferred to normal skin can be neutralized in the sensitized site. That is, after the corresponding antigen is injected several times into the sensitized area of the skin a positive reaction is no longer obtained. However, reagins do not neutralize in vitro their related allergens, while anaphylactic antibodies are neutralized in vitro by their related antigens.

IMMUNOLOGY

As will be seen later, little is understood about the mechanism of the immunologic reaction in acquired allergy, such as contact dermatitis, drug allergy, and tuberculin sensitivity. Most of the information which we have applies to the atopic or familial type of allergy. It is likely that the clinical manifestations of atopy are brought about by a reaction or union between the allergen or atopen and its specific antibody, known as reagin.

Characteristics of Allergen. The allergen is in all probability a true antigen. The nature of the active principle in the allergen has not as yet been definitely determined, because in some allergens it seems to be a nitrogenous substance, while in other allergens the removal of all protein and nitrogenous fractions seems to affect the activity of the allergen very little. There is evidence that antigens can pass through the human placenta.

Characteristics of Reagin. Specific antibodies or reagins are found with great constancy in atopic disorders (asthma, hay fever, eczema). They have definite characteristics which have been well established by Coca:

1. Reagins are skin-sensitizing antibodies, that is, *when present in the blood they are also found attached to the skin*, so that when the corresponding allergen is injected into the skin of a patient who has the specifically related reagins, local exudation results, giving rise to a wheal. Use is made of this phenomenon for diagnostic purposes. As was stated before, nonatopic persons can occasionally produce reagins, but the reagins last but a short time in these people and, according to present evidence, play little or no role in the production of the patient's symptoms

2. Another characteristic property of reagins is the possibility of transferring them to normal skin which subsequently becomes sensitized to the related allergen. This

local sensitization lasts from a few days to a month. This is referred to as the Prausnitz-Kustner or passive transfer reaction. The technic of this test is as follows: One-tenth of a cubic centimeter of the previously Seitz-filtered and now sterile serum of a patient who is sensitive, let us say, to fish, is injected intradermally into the skin of a normal, nonallergic person About 6 to 10 hours later, after the reagins have had time to attach themselves to the cells of the skin, a small amount of allergen (fish in this case) is injected into the sensitized site. Shortly thereafter one obtains a positive reaction as evidenced by the formation of a wheal. This positive reaction can be taken as proof that the transferred serum contained anti-fish reagins. It is therefore a technic which can be employed for clinical diagnostic purposes as well as for the purpose of determining the presence of reagins. In performing the test, needless to say, certain precautions must be followed. The Wassermann reaction of the patient should be negative. A control, using an intradermal test with the allergen (in this case fish), is performed on the substitute to make certain that he is not sensitive to fish. Finally, it is well to warn the substitute not to eat the foods to which one suspects the patient might be sensitive, for, as has been demonstrated, sufficient food protein may be absorbed through the gastro-intestinal tract and reach the substitute's skin to give rise to positive reactions in each of the sensitized sites The test is of practical value in the indirect testing of infants and in the testing of eczematous patients when no uninvolved skin is available.

3 Reagins transferred to normal skin can be neutralized in the sensitized site. That is, after the corresponding antigen is injected several times into the sensitized area of the skin a positive reaction is no longer obtained. However, reagins do not *neutralize in* vitro their related allergens, while anaphylactic antibodies are neutralized in vitro by their related antigens.

4. *The reagin is a true antibody; it is produced by antigenic* stimulation. In support of this view can be cited reports of the experiment performed by Coca and Grove relative to the testing of hay-fever patients in Germany—an experiment which was cited earlier in this chapter. Furthermore, the reagin content of the blood of hay-fever patients is frequently increased during prophylactic hay-fever treatment. This may be due to the antigenic stimulation of the pollen extract.

5. Reagins are specific for their respective allergen. Thus, if a normal skin is sensitized by passive transfer, with the serum from a patient sensitive to two substances, and then the local site is desensitized with only one of these substances, the area will still be sensitive to the second allergen. It is, therefore, possible to neutralize the reagins against one substance, while the unrelated reagins remain unaffected in the sensitized site.

6. Reagins are not precipitating antibodies, for the addition in vitro of allergen to a reagin-containing serum does *not bring about the phenomenon of precipitin formation.* Precipitin formation does not accompany the presence of reagins as in the case of anaphylactic antibodies.

7. The atopic reagin does not sensitize the guinea-pig uterus. An attempt to sensitize passively the guinea-pig uterus or the guinea-pig skin with atopic reagins has not succeeded It has not been possible to perform passive sensitization of guinea pigs with reagin-containing human serum. Nor is it possible to sensitize the human skin with the serum of an anaphylactically sensitive guinea pig.

8. Reagins are thermolabile Anaphylactic antibodies are thermostable

9. Reagins do not mediate complement fixation in mixture with related antigen. The characteristics of reagins as described above are definitely different from those described in a previous chapter with reference to anaphylactic anti-

bodies which play such an important role in mediating anaphylaxis in animals (see Table 1).

10 Reagins do not pass through from mother to offspring because they have not been demonstrated to exist in cord blood.

TABLE 1

COMPARISON BETWEEN ANAPHYLACTIC ANTIBODIES AND REAGINS *

Anaphylactic Antibodies	*Reagins*
Similarities	
Specific for related antigen	Specific for related allergen
Result from antigenic stimulation	May result from antigenic stimulation
Capable of producing passive sensitization	Capable of producing passive sensitization
Neutralizable in guinea-pig uterine strip (Dale-Shultz technic)	Neutralizable in the sensitized site
Differences	
Comparatively short lived (weeks)	Usually last over a long period of time (years)
Associated with precipitin formation	Unassociated except in rare instances of acquired allergy with precipitin formation
Not capable of sensitizing human skin	Skin-sensitizing antibodies
Neutralized in vitro by the related antigen	Do not neutralize the related antigen in vitro
Capable of sensitizing guinea-pig uterus	Not capable of sensitizing guinea pig uterus
Cannot sensitize human skin	Cannot sensitize guinea-pig skin
Thermostabile	Thermolabile
Complement fixation property demonstrable in mixture of anaphylactic antibody and related antigen	Mixture of reagin and related antigen does not show complement-fixation property

* Based on work done principally by A F Coca

Determination of Reagin Content in Serum. (1) DILUTION TEST (Cooke). This test is intended to determine the activity and the amount of reagin present in a given serum. It is conducted as follows. various dilutions of reagin-containing serum are injected into the skin of a substitute; 12 hours later equal amounts of the respective antigen are injected in each one of the sites. This test will determine the activity and the amount of the reagins present.

(2) NEUTRALIZATION TEST. This consists in the injection in the skin of a test subject of reagin-containing serum mixed with increasing amounts of the corresponding antigen, 24 to 48 hours later each one of the sensitized sites is tested with the same antigen Obviously, in those sites where the reagin has been completely neutralized by antigen, no reaction will occur.

These tests have been of great value in the study of the immunology of the whealing type of skin-reacting allergy of which hay fever is a good example. It is to be noted that, in conducting the neutralization test, immediate wheals are obtained in the test subject upon injecting his skin with an antigen reagin mixture However, if the reagin-containing serum of a patient who had received pollen treatment is used in this mixture, practically no local reaction occurs.

"Blocking" (Thermostabile) Antibody of Cooke. Some time ago Cooke demonstrated that more antigen (ragweed) is required to neutralize the serum of a ragweed-sensitive patient obtained after a season of treatment with ragweed extract than is required to neutralize the serum of the same patient before treatment is instituted. This increase in the amount of antigen necessary is due not to an increase in the amount of reagins formed following treatment with ragweed extract, but rather to the production of another antibody which interferes with the reaction of reagin and antigen This new interfering antibody has been termed a blocking antibody. It has been shown that this blocking

antibody is formed also in the serum of nonallergic individuals who receive injections with ragweed extract. It has certain definite properties Unlike the reagin, it is a thermostabile antibody, and, also unlike the reagin, it does not have the property of sensitizing the skin of a normal person. In reality it is a neutralizing antibody.

The presence of the blocking antibody can be demonstrated as stated above by the passive transfer test. Serum from a nontreated ragweed hay-fever patient is mixed with ragweed pollen extract and injected in a number of sites into a substitute Following such injection a local whealing reaction occurs. The serum of a ragweed hay-fever patient who has received pollen therapy is mixed with the ragweed extract and injected in another series of sites. No reactions will follow after this series of injections. This proves that the post-treated serum contains some immune substance which interferes with the union of antigen and its respective reagins. This inhibiting or blocking antibody apparently binds its antigen, preventing it from reacting with the corresponding reagins It is therefore possible to carry out quantitative studies using the passive-transfer technic, and to determine the amount of blocking (thermostable) antibodies present *in* a given serum

This may be done by sensitizing several sites with equal amounts of post-treated *serum* Each site is then injected with varying dilutions of antigen. Since the inhibiting or blocking antibody binds antigen, it is obvious that the passive transfer reaction will be greater in those sites in which free antigen is left to react with the corresponding reagins. If these passively sensitized sites are injected for the second time with ragweed extract, positive reactions will be obtained in the sites in which the original amount of injected antigen was completely neutralized or bound by the blocking antibody, leaving the reagins free to react with subsequently added antigen On the other hand, no reac-

tion will occur on reinjection of antigen into those sites in which previous positive reactions occurred. This results from the fact that no reagins have been left to unite with the antigen injected for the second time. The blocking antibody may also be detected by the precipitin reaction. This is done in the following manner: Rabbit-ragweed antiserum is produced by suitable injection of a rabbit with alum-precipitated ragweed-pollen extract. The serum of a ragweed hay-fever patient is obtained before and after the institution of treatment with ragweed extract. This serum is heated to 56° for four hours to destroy the reagins. Both heated sera are then treated in separate test tubes with ragweed extract. Dilutions of each of these mixtures are added to rabbit antiserum (namely, a serum which contains anti-ragweed pollen precipitins). Clouding results in the test tubes because of the presence of precipitins Controls are also run. The blocking antibodies found in any of the test tubes will unite with the ragweed, thus leaving less ragweed to produce the precipitation reaction. Since the serum obtained after a season of treatment with ragweed contains more blocking antibodies, this serum will produce less precipitation.

CLINICAL MANIFESTATIONS

The clinical manifestations of allergy depend largely on heredity, the location of the shock organ, and the nature of the allergen. Heredity predetermines to some extent the type of allergy which the individual will develop. The symptoms are determined also by the location of the shock organ, whether it is the skin, the mucous membranes of the nose, the gastro-intestinal tract, or the bronchi. The nature of the allergen is also of some importance For example, poison ivy will give rise to contact dermatitis, while an inhalant, such as pollen, will produce hay fever. Following is a list of allergic conditions:

Eyes. Edema of retina, eczema of the lids, edema of the lids, conjunctivitis, vernal catarrh, hay fever.

Nose. Hay fever, allergic rhinitis

Bronchi and Lungs. Allergic cough, bronchial asthma.

Skin Urticaria, angioneurotic edema, contact dermatitis, atopic dermatitis, erythema nodosum, erythema multiforme, dermatophytosis, purpura hemorrhagica.

Gastro-intestinal Tract. Canker sores, acute gastro enteritis, certain types of mucous colitis, cyclic or periodic vomiting

Genito-urinary Tract. Some instances of essential hematuria, irritable bladder, cystitis

Joints. Intermittent hydro-arthrosis, certain types of arthritic involvement

Central Nervous System. Some instances of migraine, convulsive or epileptiform variants, some forms of the Ménière syndrome

Blood Dyscrasias. Agranulocytosis due to drugs (amidopyrine, etc.)

Many allergic patients will show, in addition to their typical allergic manifestation, generalized systemic disturbances which may be referred to as toxic. These consist of excessive fatigue, depression, tendency toward sleepiness, and headache Occasionally patients have complained of such symptoms following an excessive dose of pollen extract These symptoms are also seen in many patients presenting a food allergy with or without gastro-intestinal manifestations

COMPARISON WITH ANAPHYLAXIS

It is obvious from what has preceded that there are definite points of difference between the anaphylactic antibody (which mediates the anaphylactic reaction) and the reagin (the antibody associated with familial allergy or atopy) In the same manner one may indicate certain points of

difference between anaphylaxis and allergy, differences which seem sufficiently marked to divide the two phenomena under separate names. On the other hand, when these differences are analyzed more critically they seem less real, and this has prompted another school of thought (Zinsser, et al.) to indicate that there is a very close parallelism between allergy and anaphylaxis, and that in reality they are probably one and the same manifestation. The student of allergy may have his choice as to which of the two views he wishes to adopt, provided he is aware of the facts involved in the discussion. The author sees no valid objection, however, to the application of the term anaphylaxis to the phenomenon of hypersensitivity in lower animals and the use of the term allergy to denote a similar condition in the human. The two phenomena are based on immunologic mechanisms which in many ways are similar and which for practical purposes may be considered identical, but which for the sake of clarity and better understanding must be classed separately in a discussion of this sort.

Points of Difference. (See Table 2.) 1. Anaphylaxis can always be produced at will, experimentally, in lower animals. Such a procedure cannot be carried out successfully in the human. It is no doubt true that experimental production of anaphylaxis succeeds much more frequently than the experimental production of acquired allergy. Yet those who regard the two phenomena as one point out that both the lower animals and the human do not become easily sensitized to a substance such as pollen to which they are commonly exposed Both the lower animals and the human are, however, easily sensitized to unusual proteins—animals, let us say, to egg white, and the human to horse serum. The few individuals who develop a sensitivity to substances such as wheat and eggs, with which they come in daily contact, represent a relatively small group of people who are atopically allergic.

TABLE 2

DIFFERENCES BETWEEN ANAPHYLAXIS AND ALLERGY *

Anaphylaxis	*Allergy*
May be produced easily in the laboratory	Not easy to produce at will
Not hereditary	Hereditary in the familial group
Desensitization possible	Desensitization not possible
Exciting agent always antigenic	Exciting agent may be a non-protein
Anaphylactic antibody is the characteristic antibody	Reagin is the characteristic antibody
Shock organ differs with species but is identical in all members of the same species	Shock organ differs with individuals
Successive nonfatal anaphylactic reactions are brought on by the administration of multiple doses of antigen	Successive positive skin reactions are brought on in the passively sensitized site by the administration of the same amount of allergen

* Adopted from Coca with slight changes.

2 The element of heredity plays no role in anaphylaxis.

3 Complete desensitization, which usually does not fail in anaphylaxis, cannot be carried out in allergy Successful treatment does not usually reduce markedly the sensitivity of either the skin or the conjunctiva Patients who are treated for hay fever will frequently show a decrease in the size of the skin reaction The reagin content of the blood in most instances is increased as a result of treatment For this reason the process of treatment has been referred to as one of hyposensitization

4. The exciting agent in anaphylaxis is always an antigenic substance and must be a soluble protein. In atopy

this is not necessarily the case, for many nonprotein substances (such as drugs) are capable of acting as allergens. This would include a large group of allergies due to drugs and the group of contact dermatitis due to local agents. But it has been shown that in any of these instances where the allergen is nonprotein in nature the sensitivity develops from a union between this antigen and the body proteins, giving rise to an antigen that has been called a hapten.

5. The antibody in anaphylaxis is the anaphylactic antibody. The antibody in atopy is the reagin. These antibodies differ in fundamental characteristics.

6. The shock organ in anaphylaxis is always the same for a given species. In allergy the shock organ varies with each patient, and may differ even in the same individual in response to different allergens.

Points of Similarity. (See Table 3.) 1. Smooth-muscle spasm or contraction is part of the picture of certain forms of allergic manifestations such as bronchial asthma. The same functional pathology, that is, bronchospasm, is involved in anaphylactic shock in guinea pigs. Smooth-muscle involvement is part of the anaphylactic picture in rabbits, involving contraction of the pulmonary arterioles and in dogs involving contraction of the hepatic vein. The shock tissue in anaphylaxis differs with each species because of certain anatomic variations. Thus smooth muscle is highly developed in the bronchial tree of the guinea pig, in the pulmonary arterioles of the rabbit, and in the hepatic veins of the dog.

2. Complete desensitization is of course possible in anaphylaxis. It cannot be produced in allergy, but this may well be due to our inability to administer a suitably large dose of antigen to a sensitive human being because of the danger of a severe or even fatal constitutional reaction Clinical improvement in hay fever following treatment with pollen extract may well be due to local tissue desensi-

tization by neutralizing the reagins attached to the cells of the shock tissue This could occur in spite of the fact that such individuals have a larger number of circulating antibodies (reagins) following treatment.

TABLE 3

SIMILARITIES BETWEEN ANAPHYLAXIS AND ALLERGY *

Anaphylaxis	*Allergy*
Smooth-muscle spasm is the characteristic reaction	Smooth muscle spasm is found in bronchial asthma
Complete desensitization	Local tissue desensitization may take place in the treatment of hay fever
Arthus phenomenon	Arthus phenomenon has its counterpart in local tissue sensitivity (serum allergy)
Bacterial anaphylaxis is possible	Bacterial allergy also exists
Anaphylactic antibodies occur in response to a sensitizing antigenic substance	Reagins similarly develop from antigenic stimulation
Some evidence of manifestations of sensitivity in animals governed by a hereditary influence The absence of conclusive proof does not exclude heredity as a factor	Heredity plays an important role
Previous contact essential	Previous contact important
Mechanism based on liberation of histamine like substance	Mechanism thought to be the same as in anaphylaxis
Passive sensitization possible	Passive sensitization of local skin site possible Sensitivity transmitted occasionally by blood transfusion

* Based on work done principally by A F Coca

3. The phenomenon of passive sensitization in anaphylaxis is analogous in the human to the passive skin transfer and the transmission of allergy as a result of blood transfusion; as to the latter, there are a number of recorded instances in which a nonallergic recipient received blood from an allergic donor and subsequently became sensitive, at least for a short time, to the same substance to which the donor was allergic.

4. The Arthus phenomenon described as a form of local anaphylaxis in rabbits may also have its counterpart in the human. The subcutaneous or intramuscular injection of *horse serum in an individual who has received horse serum* before may give rise to a marked local reaction which in some reported instances is accompanied by local swelling, gangrene, and necrosis, not unlike the reaction observed in the Arthus phenomenon in rabbits.

5 Bacterial anaphylaxis is possible. Animals may be rendered anaphylactically sensitive to bacterial proteins. This would seem to be analogous to bacterial allergy in man even though it is not possible in man to produce specific positive skin reactions or constitutional reactions by the administration of bacterial (respiratory) vaccine. This may be due in part at least, however, to improper and imperfect methods of preparation of vaccines, the protein nature of which is somewhat changed from that originally found in the tissues.

6. It is pointed out that anaphylactic sensitivity is always accompanied by the presence of anaphylactic antibodies, *while it is not always possible to demonstrate the presence of antibodies in allergy (drug and tuberculin allergy, etc.)* Zinsser * believes that the presence of antibodies is not particularly important in connection with this discussion, and

* Zinsser, H., J F Enders, and L D. Fothergill Immunity Principles and Application in Medicine and Public Health, New York, The Macmillan Co, 1939.

states that "It is a well-known fact that even in true anaphylaxis an animal may be highly sensitive without containing antibodies in its blood." The phenomenon of anaphylaxis is largely a cellular phenomenon, and the presence or absence of circulating antibodies is not necessarily of great importance according to this view. He concludes by saying "It is quite apparent therefore that although we cannot at the present time identify reagins with the well-known antibodies, yet there are so many points of close similarity and they must both be regarded as specific reaction bodies to a sensitizing antigenic substance."

Carlson and Caulfield were able to sensitize guinea pigs and monkeys with potassium alum-precipitated pollen extract. Their animals developed antibodies identical with reagins so that it was possible to perform passive transfer to the skin of a human using the guinea-pig serum This antibody is neutralizable by its corresponding antigen in vitro

7 The transmission of anaphylactic sensitivity *in guinea* pigs is purely a passive sensitization because of the passage of antibodies through the placenta, with the result that the offspring is always sensitive to the same substance as the mother *In the* human this is not the case because frequently the offspring will be sensitive to a substance entirely different from that which produced sensitivity in the parents This apparent difference has been explained by some on the basis of anatomic differences in the placenta of different species According to this view, the placental layer in the guinea pig separating the fetal from maternal circulation is *very thick* It permits only the passage of antibodies from the maternal to the fetal circulation, resulting in passive sensitization. The thinner placental separation in the human permits both the passage of antibodies and antigen, in this way giving rise to both passive sensitization and active sensitization in utero However, it

3 The phenomenon of passive sensitization in anaphylaxis is analogous in the human to the passive skin transfer and the transmission of allergy as a result of blood transfusion; as to the latter, there are a number of recorded instances in which a nonallergic recipient received blood from an allergic donor and subsequently became sensitive, at least for a short time, to the same substance to which the donor was allergic.

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Major allergic manifestations occur in about 10 per cent of the population. Factors which play a role in the etiology of allergy are: exposure, the type and dose of allergen, the antecedent family history, climate, and environment. In the familial or atopic allergic conditions the individual inherits the predisposition to manufacture reagins as well as a sensitive shock organ Nonallergic individuals may also manufacture reagins on suitable exposure, but these differ in many respects from the reagins found in atopic patients.

The pathology of allergy, while not typical, does include such characteristic findings as eosinophilia in the blood, tissues, and secretions, and edema of the mucous membrane and skin.

The physiology of allergy must take into consideration the influence of the autonomic nervous system involving both the sympathetic and parasympathetic. Smooth-muscle spasm is a characteristic reaction

The immune substances involved in atopy are the antigen, which is referred to as allergen, and the antibody, which is referred to as reagin. These antibodies have very definite characteristics which distinguish them from the anaphylactic antibody

The clinical manifestations may involve practically every system or organ in the body The main etiologic factors concerned in the production of these clinical manifestations are inhalants, foods, contactants, injectants, parasites (including bacteria and fungi), and physical agents

Anaphylaxis and allergy are in many ways parallel phenomena having certain common characteristics, and yet there are a sufficient number of differences still unexplained which justify the use of the two terms.

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has not been possible to demonstrate the presence of maternal reagins in the fetal circulation immediately after birth. There is also some evidence to indicate that a hereditary influence may be present in animals showing symptoms of sensitivity (sneezing, etc.) Furthermore, it is not fair to assume that just because a demonstrable hereditary factor has not been revealed in animals it does not exist in those species.

8. Contact may play a similar role in allergy and anaphylaxis. Preliminary or first contact is not always obvious in allergy It is possible for a child, for example, to receive certain proteins such as eggs through the mother's milk and thus become actively sensitized for the first time to eggs, with the result that upon first being given eggs allergic manifestations develop. Unless this possibility of a previous exposure to egg is considered one might say that there was no first contact.

9. Sensitization to physical agents has not been demonstrated in animals, but it must be pointed out that in both allergy and anaphylaxis the physiology and mechanism of production of the allergic manifestations is essentially the same: the liberation of a histamine or histamine-like substance.

SUMMARY

Allergy is a term employed to designate the specific hypersensitiveness of human beings It may be familial (atopic) or acquired. The familial group includes such clinical conditions as hay fever, asthma, eczema, allergic rhinitis, and some cases of urticaria, angioneurotic edema, and migraine. The acquired type of allergy includes (1) Serum allergy (serum sickness, accelerated serum reaction); (2) drug allergy; (3) contact dermatitis, (4) allergy to infection (parasites, bacteria, fungi), (5) allergy to physical agents (heat, cold, sunlight). It is to be noted that some instances classed under acquired allergy may also be familial.

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4

Diagnosis of Allergy

RELATION OF ALLERGY TO PRACTICE OF MEDICINE
CRITERIA FOR DIAGNOSIS
PROCEDURES EMPLOYED IN STUDY OF ALLERGIC PATIENT
PREPARATION OF EXTRACTS
LIST OF ALLERGENS
CONSTITUTIONAL REACTIONS AND THEIR TREATMENT
DISCUSSION ON ALLERGENS
SUMMARY

RELATION OF ALLERGY TO PRACTICE OF MEDICINE

Allergy is essentially a special field within the division of internal medicine. Because allergic manifestations involve the child as well as the adult, and because they may involve various parts of the body, we find the rhinologist, the ophthalmologist, the dermatologist, the pediatrician—indeed, every practitioner of medicine and surgery—concerned with allergic problems (see Fig. 3).

CRITERIA FOR DIAGNOSIS

The determination, insofar as it is possible, of the presence of the allergic state should precede the employment of the various diagnostic methods intended to reveal etiologic factors. Experience teaches that certain clinical conditions such as asthma, hay fever, and eczema are allergic. We also know that certain dermatoses and the reactions following the administration of foreign sera and drugs may also be allergic. There are certain criteria which are found

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ance of the nasal mucous membrane and conjunctivae are not sufficient for a definite diagnosis.

Skin Tests. Allergic patients usually give positive reactions when the skin is tested with properly prepared extracts.

Response to Epinephrine. This is a good therapeutic test for allergy. Relief from annoying nasal or asthmatic symptoms following the administration of epinephrine or ephedrine constitutes additional proof of allergy.

Clinical Exposure Symptoms may be brought on or may be exaggerated by the ingestion of certain foods, or by the intranasal and conjunctival application of raw materials or of extracts of such materials (pollen).

PROCEDURES EMPLOYED IN STUDY OF ALLERGIC PATIENT

History. The allergic history forms one of the most useful parts of an allergic investigation and, in experienced hands, will frequently supply [illegible] and leads of prime im-

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ways

habits over a long period of time. The following form may be employed as a guide in the taking of an allergic history

Chief Complaint. State the chief symptoms as presented by the patient.

Analysis of Chief Complaint. Age and mode of onset of the initial attack, time of-onset (day or night), duration, severity, frequency, and progress of condition up to the last attack The patient's own opinion of the causative and contributing factor or factors idiosyncrasy to foods, sensitivity to dust, etc. Include a detailed analysis of various symptoms, such as. eye—lacrimation, itching, pain, redness; nose—coryza, congestion, obstruction to nasal breathing, itching, sneezing, chest—dyspnea, wheezing, cough, expec-

in those allergies which are familial (atopic). These may be stated as follows:

Heredity. The atopic patient invariably gives a family history of allergy.

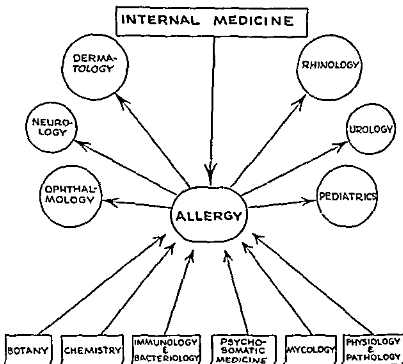


Fig. 3. Relation of allergy to other sciences and branches of medical practice.

Allied Allergic Manifestations in Same Patient. It is not uncommon for the asthmatic patient to present a history of hay fever, eczema, or hives, or for the patient with nasal allergy to have typical asthma.

Eosinophilia is found in the blood, sputum, or nasal secretions. This finding is of special value in doubtful rhinologic and eye cases where the history and the appear-

quire also for the presence of past medical conditions, operations, and the administration of sera for prophylactic or therapeutic purposes.

Family History. Inquire as to the presence of any allergic diseases in antecedents. Do any of the patient's children have allergic diseases?

Physical Examination. Every allergic patient should receive a careful and thorough physical examination in order to exclude conditions which may complicate or be confused with the original allergy. For example, one must consider in bronchial asthma the possibility of pulmonary tuberculosis, cardiac asthma, mediastinal-gland enlargement, or renal disease.

Diagnostic or Sensitization Tests. These tests are performed for the purpose of determining the presence of sensitivity. The procedure includes more than what are popularly referred to as skin tests Skin tests constitute only part of an allergic survey The indiscriminate routine performance of a series of skin tests means little or nothing On the other hand, if these tests are properly performed with fresh, potent, and biologically tested extracts, and if the tests are interpreted critically and correctly, they constitute an important link in the chain of evidence which may unearth the cause of the patient's allergy. Such testing may be done in several ways and each method has its own advantages and indications.

Skin Tests. Skin tests are performed with properly prepared extracts on the arm or back of the patient in one of several ways

Scratch Test (see Figs 4, 5, and 6). Clean the skin of the forearm or of the back with alcohol. With a blunt knife or needle make a series of scratches, each one-eighth of an inch long, through the outer epidermis, being careful to cause no bleeding The extract, especially prepared for the scratch test, is added to the scratch, and 10 to 15 min-

toration; skin—location of lesion, weeping, itching, redness, distribution. State the character of the nasal secretion (*watery or purulent*); *effect of irritants such as tobacco* smoke, camphor, tar, paint, etc.; seasonal occurrence of symptoms. The presence of sensitivity to drugs, such as *aspirin, phenolphthalein, insulin, quinine, belladonna, the* halogens (bromides and iodides), the metals (mercury and arsenic); effect of environment or climate. Does epinephrine give relief?

Social History. Occupation of the patient and his family, as for example· animal contacts in peddlers and stablemen, contact with flour in the case of bakers or housewives, use of insect powder by janitors, contact with drugs such as flaxseed and salicylic acid in the case of pharmacists, use of chemicals such as formalin and phenylhydrazin by laboratory workers, and exposure to furs by furriers. *Certain foods* such as vegetables and fruits are seasonal, and may be responsible for the seasonal occurrence of allergic symptoms. *The acquisition of new bedding, pillows, furniture,* rugs, garments, and toys (stuffed animals may contain rabbit hair) may be important Mohair, obtained from goat hair, is used for upholstering of automobile seats, railway cars, and furniture Rugs are made from cotton, wool, goat hair, and occasionally (as in oriental rugs) from camel hair. The patient's habits and hobbies may be of importance. Inquire as to the type of face powder, soap, perfumes, and tooth pastes which may contain rice, orris root, or corn Contact with such plants as poison ivy, primrose, and chrysanthemums, *and exposure to heat, cold, and sunlight may have* a bearing on the patient's symptoms Are there any animal pets in the home of the patient? Does change in environment influence the condition?

Past Medical History. Inquire as to allergic diseases in infancy, such as eczema, hives, cyclic vomiting, gastric symptoms, bronchitis, repeated colds, asthma, and migraine. In-

quire also for the presence of past medical conditions, operations, and the administration of sera for prophylactic or therapeutic purposes.

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utes are allowed to intervene before the reaction is read. This method of testing has the advantage of giving rise to a minimum of constitutional reactions, and is therefore safer in the hands of the general practitioner.

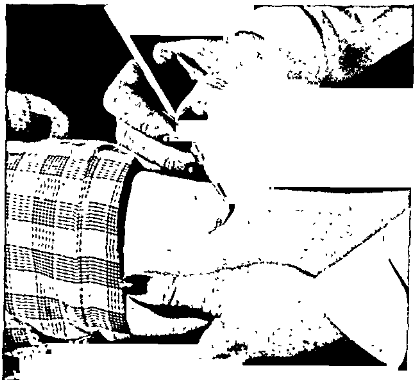


Fig. 4. Scratch Test. Clean skin of forearm or back with alcohol. With a blunt knife or needle, make a series of scratches, each one-eighth of an inch long, through the outer epidermis, being careful to cause no bleeding.

Intradermal Test (see Fig. 7) This consists in the injection, between layers of the skin, of a small amount, usually 0.01 cc., of a specially prepared liquid extract of the suspected substance. A tuberculin syringe and a 26-gauge, ¼-

or $\frac{3}{8}$-inch rustless needle is used for the purpose. These are sterilized by boiling. The skin is cleaned with alcohol and 10 to 12 injections are made up and down the arm in two rows, the injections being about one inch apart. This



FIG. 5. Scratch Test (*continued*). Application of testing material in form of either a solution in glycerin or a powder after one drop of N/10 (one-tenth normal solution) sodium hydroxide has been added to the scratch.

method is cleaner, less painful, more accurate, and more rapid than the scratch test. However, it yields a greater percentage of false-positive reactions, and occasionally it may give rise to a serious constitutional reaction It is of greatest value in hay fever, asthma, and in some cases of atopic

dermatitis. It is of no value in contact dermatitis and drug allergy. The appearance of localized edema or a wheal, *especially accompanied* by pseudopods and a surrounding area of erythema, indicates a positive reaction. This reaction is read as slight, moderate, or marked, depending on the size of the wheal and the number of pseudopods. Occasionally the reaction may be doubtful or slight, but within 24 hours a definite positive reaction may result. This is known as a delayed reaction. False-positive reactions, which are referred to as nonspecific reactions, occur not infrequently in a highly sensitive skin, while a refractory skin will fail to give a positive reaction even where clinical sensitivity exists. Furthermore, the reaction depends also on the nature, the amount, and the concentration of the extract employed in testing.



FIG. 6. Positive Scratch Test. Note wheal surrounded by pseudopods and compare with negative control below.

Patch Test (see Figs. 8 and 42). The skin of the arm, forearm, or back is washed. The suspected material is placed on the skin, covered with a small square of cellophane, and held down with a strip of adhesive, scotch tape, or collo-

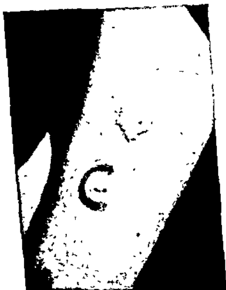


FIG. 7. Positive Intradermal Test. *Note C control Positive reaction* marked by increase in size of wheal, surrounding erythema, and pseudopods

dion The reaction is read in from one to four days. The patch test is of value in such conditions as poison ivy and various forms of contact dermatitis. The name of the material with which the test is made should be written on the adhesive, or the test may be numbered for identification. If the material is a liquid substance it may be placed on a small square of blotting paper or linen next to the skin On

top of this a piece of cellophane is placed. Thus the zone of skin which comes directly in contact with the cellophane is separated from the portion of skin touched by the test-

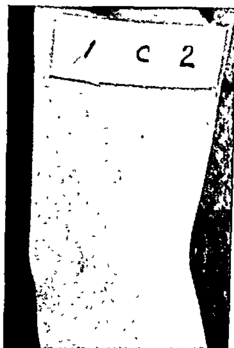


FIG 8 Technic of Patch Test. Material held in place under small square of cellophane by adhesive. C = control in center. For positive patch test, see Figure 42

ing substance. *This is necessary because occasionally patients* may be found who are sensitive to adhesive, and the reaction may be difficult to read unless the test is performed as stated above

It has been found that it is possible for a patient to give a negative patch test when the test is performed at a point

distal to that where the original lesion occurs. If the patch test is performed near the lesion a positive reaction may be obtained. Because contact dermatitis may involve the mucous membranes as well as the skin one must keep in mind the fact that patch tests in such cases performed on the



FIG 9. Technic of Passive Transfer. Withdrawal of blood from allergic patient under sterile precautions

skin may or may not be positive. There are some reported instances of sensitivity of the mucous membranes of the mouth due to contact with dental plates Patch tests performed on the skin with the material contained in these dental plates have given a positive reaction. In another instance a patient sensitive to tobacco developed canker sores and ...

...g a pipe. Patch tests done with tobacco in this instance were negative, and yet the patient had a definite mucous-membrane sensitivity to tobacco or its products.

Indirect Test (*Prausnitz-Küstner*) (*Passive Transfer*) (see Figs. 9, 10, and 11). The skin of a normal person is sensitized by the injection of 0.1 cc. of the serum of the patient.

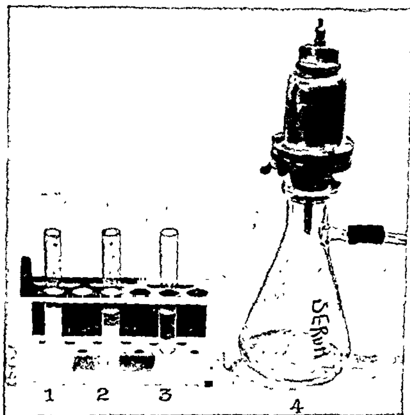


Fig 10. Technic of Passive Transfer (*continued*). (1) Blood from allergic patient; (2) separation of serum from blood, (3) patient's serum; (4) sterilization of serum by passing through a Seitz filter.

Twenty-four hours later an extract of the suspected protein is injected into the site. The appearance of a wheal is indicative of the sensitivity of the patient to that protein. The control with the same material on the substitute should be

negative This test is very useful in cases in which it is not possible to test the patient directly—in infants, for example, or if the skin of the patient is extensively involved in a severe dermatitis or dermographia.

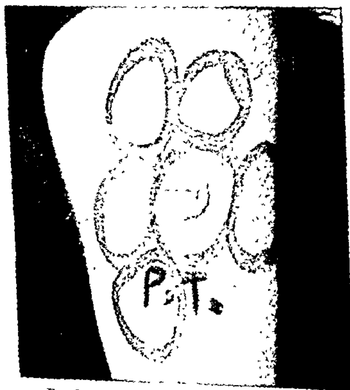


Fig. 11. Technic of Passive Transfer (*continued*). Six local skin sites of arm of a nonallergic substitute are injected with serum of patient. Each site is tested 24 hours later with extracts of allergens. Note positive reaction in center, indicating presence of transferred reagins to material used in testing.

Ophthalmic Test (see Fig. 12). This test, a good corroborative procedure, is performed by placing in the conjunctival sac a drop of the extract or a few grains or small amount of the dry, raw material which one suspects to be the offending agent. Within a few minutes, if the test is

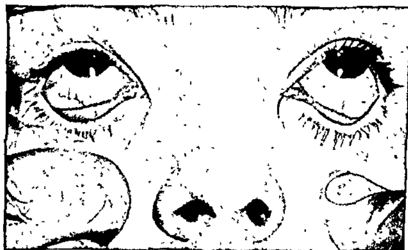


Fig. 12. Technic of Ophthalmic Test. Allergic conjunctivitis and rhinitis in a young girl markedly sensitive to orris root (cosmetics). Note the marked positive ophthalmic test (O D) to weak solution of orris root.

positive, there is marked congestion of the conjunctival vessels with redness of the eye, lacrimation, and itching. As a rule mucous membranes are less sensitive than skin. After repeated tests, both the skin and mucous membranes may become temporarily refractory.

Nasal Test. This test is performed in the same manner as the ophthalmic test. It is sometimes referred to as the sniff test.

Elimination Tests. Trial or elimination tests are of great value in arriving at an etiologic diagnosis of a pa-

tient's allergy. These trial tests may be applied to various inhalants, contactants, and injectants. The substance under suspicion is eliminated from the patient's environment. If improvement follows, we conclude it to be of etiologic importance Elimination of inhalants may be brought about effectively by placing the patient in an air-conditioned room for from 24 to 48 hours The elimination or trial tests may also be employed with respect to the diagnosis of food allergy. This is particularly necessary since, as has been stated before, skin tests to foods are not always reliable. The skin tests may be used, of course, as the basis for the determination of the elimination diet. The principle involved is that of placing the patient on a diet consisting of only a very few foods which we know are not likely to cause the allergy Elimination diets devised by Rowe (see Table 4) consist of four diets which may be given to the patient successively or alternately Diets 1 and 2 contain foods which are very rarely allergenic. The *patient is* started on Diet 1, and if he gets along well he may be placed on Diet 2 later If desirable therapeutic results are not obtained he may be changed to Diet 4, which is composed of milk alone, and if symptoms disappear, *then* constituents of Diets 1 and 2 *may* be added gradually and slowly

In some *instances* the patient is requested to keep a food diary (see *Table* 5) over a period of four to five weeks in order to discover any possible relation between the diet and his allergic symptoms

Laboratory and Special Examinations.

1 URINE—routine examination

2 BLOOD COUNT *to* determine presence of anemia and eosinophilia.

3. EXAMINATION OF SPUTUM for Curschmann's spirals and eosinophils In suspected cases a search is made for the tubercle bacillus

TABLE 4

ELIMINATION DIETS (ROWE) *

Diet 1	Diet 2	Diet 3	Diet 4
Rice	Corn	Tapioca	Milk †
Tapioca	Rye	White and sweet potato	
Rice biscuit	Cornpone	Lima bean-potato bread	
Rice bread	Corn-rye muffin	Soya bean-lima bean bread	
Lettuce	Rye bread	Beet	
Spinach	Ry-Krisp	Carrot	
Carrot	Tomato	Lima bean	
Beet	Squash	String bean	
Artichoke	Asparagus	Tomato	
Lamb	Pea	Beef	
Lemon	String bean	Bacon	
Grapefruit	Chicken	Lemon	
Pear	Bacon	Grapefruit	
Cane sugar	Pineapple	Peach	
Wesson oil ‡	Peach	Apricot	
Olive oil	Apricot	Cane sugar	
Salt	Prune	Olive oil	
Gelatin	Cane sugar	Wesson oil ‡	
Syrup made of maple sugar or cane sugar flavored with Mapleine or maple sugar	Mazola oil	Gelatin	
Olive	Wesson oil ‡	Salt	
Pear butter	Salt	Olive	
	Karo corn syrup	Maple syrup or syrup made with cane sugar flavored with maple	
	Gelatin		

* From Rowe, Albert H Food Inhalant and Other Clinical Allergy, Philadelphia, Lea & Febiger, 1937

† Milk should be taken up to two or three quarts a day Tapioca cooked with milk and sugar also may be taken

‡ Wesson (cottonseed) oil is included in all diets With allergy to cottonseed as shown by skin test or history this must be excluded and a cottonseed-oil shortening such as Crisco must not be used If allergy to cane sugar is suspected beet sugar or corn glucose may be used.

TABLE 5 (Courtesy, Ralston Purina Co., St. Louis, Mo.)

FOOD DIARY

Name ____________________ Address ____________________

From __________ To __________

FOOD	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S

REACTION	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S

Start the diary on Sunday, listing in the Food column all foods eaten that day, checking them in the first S column. The following day record all new foods eaten, checking them under the M column. Be sure to also check foods previously listed if you have eaten them again on succeeding days.

In the reaction column at the bottom of the page are listed possible allergic symptoms. As these symptoms occur, check them under the day on which they occurred.

4. Gastric Analysis. Some allergic cases show achlorhydria and are benefited by the administration of hydrochloric acid.

5. Nasal secretions—examined for eosinophils

6. Leukopenic index to determine the leukocyte response (drop) to the ingestion of foods to which the individual may be allergic.

7. Serology.

8. Blood Calcium. A series of cases studied by the author several years ago failed to show the presence of hypocalcemia in allergic conditions.

9. Roentgenogram of chest to reveal presence of pulmonary pathology (tuberculosis, bronchiectasis) and to determine the size of the heart in cases suspected of having cardiac disease.

10. Electrocardiographic study in all cases of bronchial asthma where differential diagnosis from cardiac asthma is under consideration.

11 Determination of vital capacity in asthma Vital capacity has been described as the greatest voluntary expiration following the deepest inspiration. It is definitely decreased in bronchial asthma and in pulmonary emphysema. This decrease is due not only to the blocking of the bronchi and bronchioles but also to interstitial fibrosis and pulmonary edema. The determination of vital capacity in asthmatic patients gives an indication of the extent of the asthma and pulmonary emphysema It also forms a valuable adjunct to treatment since it serves as an objective test in following the progress of the condition.

12. Nose and Throat Examination. It is advisable to give every patient with evidence of nasal or pulmonary allergy the benefit of a complete and careful examination pertaining to the nose, throat, and sinuses.

13. Dermatologic Examination. Cases suspected of skin allergy should be seen first by a competent dermatologist to

rule out a nonallergic skin condition before an allergic investigation is undertaken

PREPARATION OF EXTRACTS

Properties of an Ideal Extract. Properly prepared extracts of various allergens are employed in performing the sensitization tests referred to above. There are numerous methods of preparing such extracts. All these methods have the same purpose in view—namely, obtaining an allergen which is biologically potent and specific (on skin testing), and one which will retain its potency for a long period of time. This is an especially serious problem when testing for sensitivity to foods, for such skin tests are frequently not very reliable. This may be due to the manipulation of the food in the preparation of the extract or to the fact that the extract in many instances is nonspecifically irritating to the skin. The *p*H of the food extract and the rapidity with which the active allergen in these extracts (especially in fruits and vegetables) deteriorates is responsible for the unreliable results obtained in food testing. In some instances a scratch test with a fresh fruit juice will give rise to a positive reaction in a clinically sensitive patient who had a negative skin reaction when tested with a carefully prepared extract of the same food.

Steps in Preparation (see Figs 13 and 14). It is obvious that the most desirable way of determining sensitivity is to expose an individual to *contact* with the suspected substance From a clinical viewpoint this is not always practical. Hence the necessity of using specially prepared extracts In order to perform the tests accurately an extract of a substance should be available in a form representing as nearly as possible the original substance We do not know definitely what the active principle is in the allergen. In all probability it is a water-soluble protein Hence, in

preparing extracts, the original substance, whether it be a food or an inhalant such as pollen, is subjected first to a defatting process by washing it with ether. Toluol is added

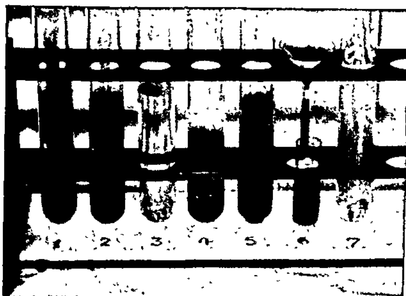


Fig. 13. Preparation of Testing Extracts (1) Dust collected from vacuum sweeper is (2) washed with ether. (3) The ether is decanted. (4) Toluol is added. (5) Extracting fluid is added and allowed to stand for 24 to 48 hours. (6) The filtrate is separated. (7) The extracted material is dialized by placing in tube of cellophane.

in order to inhibit bacterial growth. The steps which follow involve extracting the material with some watery solution—preferably one that is alkaline—because an alkaline fluid makes it easier for the protein to go into solution.

The aqueous fluid used for the extraction of most substances consists of a combination of two solutions referred



Fig 14 Preparation of Testing Extracts (*continued*) (8) The dialized solution has been concentrated by evaporation. (9) Sterilization is effected by passing through a Seitz filter. (10) Final liquid extract is bottled in sterile vial and culture controls are run (11) Extract may be preserved by drying (cryochemed).

to as buffer saline solution. These are two stock solutions, as follows *:

Solution 1:	NaCl	50 00 Gm.
	KH_2PO_4	3.63 Gm.
	$Na_2HPO_4 \cdot 12H_2O$	14 31 Gm.
	H_2O up to 1000 cc.	

Solution 2: Carbolic acid 4 per cent

Buffered saline solution has a *p*H of 7.

These two solutions are mixed in equal quantities, and one part of the resulting mixture is diluted with four parts of distilled water. The resulting solution (referred to as *buffer saline "ready for use")* is employed for the extraction and dilution of various allergens (non-juicy vegetables, fruits, epithelia, nuts, rice, etc.). It is sterilized by boiling.

For the extraction of house dust, pollens, fungi, meats, fish, and orris root, Coca's "alkaline" extracting fluid is used. The formula for this is as follows †:

NaCl . . .	0.5 per cent
$NaHCO_3$ . .	0.275 per cent
Phenol	0.4 per cent

Alkaline extracting fluid has a *p*H of 8.2.

"Preserving fluid" is used in the extraction of fruit juices and vegetable juices where the dilution must be kept down to a minimum. This consists of

NaCl . .	2.5 per cent
$NaHCO_3$.	1 25 per cent
Phenol	2.0 per cent

For scratch testing one may use liquid extracts in a form considerably more concentrated than that employed for intradermal testing. Dry-powder extracts, however, are more suitable for this purpose *These are prepared by precipitating the antigen out of solution.*

* Evans, A. Jour Infect. Dis, 30:95, 1922
† Coca, A. F Jour. Immunol, 7:63, 1922

The aqueous fluids described above are used largely for the preparation of liquid extracts. The method for the most part is identical with that originally devised and improved by Cooke and Coca.

The raw material is obtained in as clean, fresh, and unchanged a form as possible In order to facilitate extraction the substance to be extracted is divided into fine particles. This is brought about by passing it through a coffee- or meat-grinder, and then pulverizing if necessary in a mortar. Fat is removed by washing with ether. Because ether is rather expensive, Strauss and Spain prefer to employ Sovasol No. 5 for the fat extraction of all antigens except pollen, fish, and meats The latter two are washed with acetone The fat solvent is removed entirely from the antigen by filtering, squeezing through a towel, and drying. The dry material is now extracted for a variable period of time with a suitable solution (see above) with the addition of a small amount of toluol to prevent bacterial growth. The antigen containing the liquid is removed from the original material by filtration through filter paper, preceded in many instances by squeezing through a fruit press or a towel In order to separate irritating and coloring substances from the extract, it is now dialyzed in a cellophane tubing which is immersed in buffered saline If it is desired to obtain a stronger extract, the dialyzed solution is concentrated by evaporation Sterilization is done by passing through a Seitz filter Before storing, a sterilization test must be performed

Many extracts must be stored in the refrigerator to prevent deterioration Glycerinized extracts retain their potency even at room temperature. It has been shown that concentrated preparations will retain their strength for a long time if stored in a desiccated (cryochemed) form.

Detailed instructions for the preparation of individual

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Detailed instructions for the preparation of individual

extracts are available in the literature. Most of the larger books on allergy devote some space to this subject.

For scratch testing, the dry-powder extract is applied to the scratch in N/10 NaOH solution. For intradermal testing, a liquid extract of the allergen is used. Alcohol, glycerin, dextrose, or phenol may be added to the extract as a preservative. Of these the most desirable is glycerin or phenol. Glycerin-saline extracts have the advantage of maintaining their potency for a long period of time. They have the disadvantage of being somewhat painful on injection. Ordinarily, pollen or other testing material is extracted in alkaline extracting fluid under toluol for several days. After that it is filtered. The extract is next sterilized by passage through a Seitz filter. Glycerin is added to the filtrate.

Standardization of Strength. The concentration of the extract is determined by one of the accepted methods of standardization, one of which is the total nitrogen determination method. The following are the dilutions employed in our allergy clinic for intradermal testing.

0.001 mg. N	—All seeds; all danders except goat; glue.
0.05 mg. N	—Chocolate, black pepper.
0.01 mg. N	—Orris, buckwheat, all nuts, all spices except black pepper and mustard.
0 1 mg. N	—Feathers, goat epithelium, silk, sheep wool, all cereals except buckwheat.
1-100 dilution	—Horse serum, insecticides, mustard.
1-10 dilution	—Tobacco, milk, coffee, tea, lima beans, green peas, all meats, fish, eggs, mushrooms, and olives.
1-5 dilution	—All fruits and vegetables except lima beans and green peas.

Stronger extracts are employed *for scratch testing. In special* instances, where a high degree of sensitivity is suspected, or in testing children, these extracts may be used in greater dilution. Or, instead of standardization by total

nitrogen determination, the extract may be diluted 1-10 and 1-100, and employed for testing or treatment in a concentration which experience teaches is safe for that particular extract. Where glycerinated extracts are employed for intradermal testing, the concentration of glycerin in the extract should not exceed 5%, since it is irritating to the skin and may yield nonspecific positive skin reactions.

The exact method of preparing an extract depends largely upon the nature of the material to be extracted. Thus the technic for the preparation of an extract of a juicy fruit varies from that for dust or orris root. In general, however, the steps outlined above are closely followed, and an effort is made to subject the original materials to as little chemical treatment as possible It is obvious to all allergists that even the most carefully prepared and assayed testing extracts are not always entirely satisfactory. However, much progress is being made in this direction. Proper control of the pH of extracts and desiccation in a vacuum may yield more potent and more stable allergens.

Equipment. Extracts should be kept in the refrigerator. Tuberculin-type syringes and hypodermic needles, 26-gauge, ¼ or ⅜ inch long, are used for intradermal testing Epinephrine 1-1,000 and a tourniquet should form part of the necessary equipment and should always be immediately available for the treatment of a constitutional reaction.

Autogenous Extracts. Whenever it is desired to have an autogenous dust extract the patient should be instructed to collect a pint of dust from the vacuum sweeper after running the sweeper over the carpets, drapes, pillows, and mattresses When one suspects the presence of some offending agent in the patient's home this suspected substance

[illegible] about [illegible] hours, the solution obtained in this way may be used in making scratch tests.

Notes on Skin Testing. For testing children and infants it is safer to resort to scratch tests. Patients suspected of hay fever should be tested cautiously with pollen, beginning with a concentration of 0.001 mg. of N and gradually proceeding to 0.01 mg. if the reaction is not very marked to the weaker dilution. No attempt should be made to test with more than one or two pollens at a sitting if one of the tests is strongly positive. Tree-pollen tests may be made first with 0.01 mg. concentration and, if negative, with a 0.1 mg concentration. If a negative reaction to a substance is obtained in a patient who is clinically sensitive to that substance, and if it is considered desirable to test him with a stronger extract, such a concentration may be used for the purpose.

Patch tests should be performed whenever indicated, according to the technic described elsewhere in this chapter. The sniff test or the conjunctival test is done with a few grains of suspected dry pollen, dropped either into the nose or into the conjunctival sac.

LIST OF ALLERGENS

Following is a list of allergens employed for the purpose of skin-testing allergic patients (see Fig. 15). The tests are done by the intradermal method. One, two, or three series of six intradermal tests are performed at a sitting. If these are negative, another series of six or 12 may be carried out at the same time. Twenty-four hours should intervene before the patient is again tested. This precaution is necessary in order to avoid constitutional reactions which may occur following several markedly positive intradermal tests. Some individuals possess a refractory skin, others, a skin which reacts quickly even to such mechanical stimuli as stroking. A notation should be made of this at the top of the blank form under the caption "Skin Reactivity." Patients who are aware of their sensitivity to certain substances are said to be

FIG 15. Skin sensitization tests.

NAME_______________________________________

SKIN REACTIVITY_________________________________

	Test	*Re-test*
Inhalants		
Cat ep		
Cattle ep		
Chicken ep		
Cottonseed		
Dog ep		
Duck ep		
Dust		
Flaxseed		
Glue		
Goat ep		
Goose ep		
Horse ep		
Kapok		
Orris root		
Pyrethrum		
Rabbit ep		
Silk		
Tobacco		
Wool		
Cereals		
Barley		
Buckwheat		
Hops		
Malt		
Oats		
Rice		
Rye		
Tapioca		
Wheat		
Meats		
Beef		
Chicken		
Lamb		
Pork		
Turkey		
Veal		
Dairy		
Cheese		
Egg		
Milk		
Drinks		
Chicory		
Chocolate		
Coffee		
Tea		
Vegetables		
Artichoke		
Asparagus		
Bean, castor		
Bean, kidney		
Bean, lima		
Bean, navy		
Bean, soy		
Bean, string		
Beet		
Broccoli		
Brussels sprout		
Cabbage		
Carrot		
Cauliflower		
Celery		
Corn		
Cucumber		
Eggplant		
Endive		
Garlic		
Lentil		
Lettuce		
Mushroom		

	Test	Re-test
Okra		
Olive		
Onion		
Parsley		
Parsnip		
Pea, green		
Pepper		
Pumpkin		
Potato, sweet		
Potato, white		
Radish		
Rhubarb		
Spinach		
Squash		
Tomato		
Turnip		

Fruits

	Test	Re-test
Apple		
Apricot		
Banana		
Cantaloupe		
Cherry		
Currant		
Date		
Fig		
Grape		
Grapefruit		
Honeydew		
Lemon		
Lime		
Orange		
Peach		
Pear		
Pineapple		
Plum (prune)		
Quince		
Raisin		
Watermelon		

Berries

	Test	Re-test
Blackberry		
Cranberry		
Huckleberry		
Raspberry		
Strawberry		

Nuts

	Test	Re-test
Almond		
Brazil		
Cashew		
Chestnut		
Cocoanut		
Filbert		
Hazelnut		
Hickory		
Peanut		
Pecan		
Walnut, black		
Walnut, English		

Spices

	Test	Re-test
Allspice		
Aniseed		
Caraway		
Cinnamon		
Clove		
Ginger		
Horseradish		
Mace		
Mustard		
Nutmeg		
Paprika		
Pepper, black		
Peppermint		
Pimento		
Poppyseed		
Sage		
Thyme		

	Test	Re-test
Vanilla		
Wintergreen		
Patch Tests		
Grass oil		
Poison ivy		
Ragweed oil		
Fish		
Anchovy		
Bass		
Bluefish		
Butterfish		
Carp		
Catfish		
Clam		
Cod		
Crab		
Flounder		
Haddock		
Halibut		
Herring		
Lobster		
Mackerel		
Oyster		
Perch		
Pike		
Salmon		
Sardine		
Scallop		
Shad		
Shrimp		
Smelt		
Sole		
Trout		
Tuna		
Whitefish		
Bacteria		
Microc cat		
Pneumo		

	Test	Re-test
Staph.		
Strep hem		
Strep. virid.		
Misc.		
Horse serum		
Indian gum		
Tragacanth		
Tuberculin		
Specials		
Pollens		
Trees .01 mg.		
Ash		
Beech		
Birch		
Elm		
Hickory		
Maple		
Oak		
Pine		
Poplar		
Sycamore		
Grasses .01 mg.		
Bermuda		
Blue		
Johnson		
Orchard		
Red top		
Rye		
TIMOTHY 001		
" 01		

	Test	Re-test
Weeds .01 mg.		
Cocklebur . . .	. . .	. . . .
Lamb's quarters .	. . .	. . . .
PLANTAIN .01	. . .	.
RAGWEED .001	. .	. . . .
" .01	. . .	. . .
Sagebrush	. . .	. . .
Sw vernal	. . .	. . . .
Thistle	. . .	. . . .
Fungi		
Alternaria	. . . .	. . . .
Aspergillus . . .	.	.
Chaetomium . .	. . .	. . .
Hormodendron	. . .	. . .

	Test	Re-test
Monilia	. . .	. . . .
Mucor	. . . .	. . . .
Oidiomycin	. . . .	. . . .
Penicillium .	. . . .	. . . .
Trichophyton .	. . .	. . . .
Yeast	. . . .	. . . .
Sniff Tests		
Plantain	. . . .	. . . .
Ragweed	. . . .	. . . .
Timothy . .	. . . .	. . . .
. . . . . .	. . . .	. . . .
.	. . .	. . .
. .	. . . .	. . . .
. .	. . . .	. . . .

______________ M.D.

clinically sensitive to them. Note of this should be made under the corresponding heading on the skin sensitization form. It should be pointed out that it is not necessary to perform all the tests listed in Fig. 15 routinely in every patient. Children and infants are naturally not tested to foods which they do not eat and are not likely to eat. Nor is there any point in testing hay-fever patients to pollens which are not found in the district in which the individual lives. Pollen-sensitive patients are tested routinely to house dust and fungi, and to the more important foods only in instances where the history is not clear or where the therapeutic results are not satisfactory Sniff tests are employed when the results obtained from skin testing to pollen contradict the history—in other words, they are used to substantiate the history. Obviously intradermal or scratch tests are not employed in contact dermatitis because the test indicated in this condition is the patch test Some allergists prefer to do "group" testing, using a biologic classification

of various allergens This method has both advantages and disadvantages Testing to bacterial extracts is not encouraged because the interpretation of the results is not always clear. To contend that allergy to bacterial proteins exists is perfectly admissible, but it does not follow that one can detect the presence of such sensitivity by skin testing with bacterial suspensions.

The interpretation of skin tests brings into play a great deal of experience This involves a knowledge of the method of preparation of the extracts one is employing. Some extracts may be more irritating than others and therefore yield nonspecific skin reactions. Some patients have highly reacting skin, while the skin of others is very refractory The extent and size of the skin reaction is not always a guide as the severity of clinical sensitivity. One plus or two plus reactions may have important clinical significance Occasionally, a reaction occurs not within 10 to 15 minutes after the test is done, but within 24 to 48 hours. This is referred to as a delayed positive reaction, which may or may not be an index to clinical sensitivity

Skin reactions, whether resulting from the scratch or the intradermal method of testing, are read usually as follows:

- −, negative, if same as control
- ±, doubtful. A stronger extract may be used in retesting
- +, one plus, slight. Wheal somewhat larger than control No pseudopods. No erythema.
- ++, two plus, moderate
- +++, three plus, moderate plus Reaction is less than 1 cm in diameter
- ++++, four plus, marked Wheal is more than 1 cm in diameter and is surrounded by pseudopods and an area of erythema.

Epinephrine reduces the extent of the reaction. Children do not yield reactions as marked as those found in sensitive adults. The skin reactions in infants are still less marked, but this should not argue in favor of eliminating the testing of infants.

CONSTITUTIONAL REACTIONS AND THEIR TREATMENT

An allergic patient may show a mild or a very severe general reaction due to the administration of an extract of a substance to which he is sensitive. Such a reaction occasionally results even after a test dose. The severity and speed with which a reaction occurs depends on the dosage and concentration of the extract as well as on the rapidity of absorption. When the extract is inadvertently introduced directly into the circulation, as when the needle enters one of the small veins, a constitutional reaction may occur. This reaction usually comes on within a few minutes or a few hours. The sooner it occurs the more severe it is likely to be. It manifests itself in the following manner: The palms of the hands, the lips, the roof of the mouth, and the nose begin to itch, and the patient begins to rub them. The face is flushed. Urticaria may appear over the entire body. The nose is congested and hay-fever symptoms develop Finally, increasingly severe dyspnea and asthmatic breathing supervene, and if treatment is not instituted rapidly, shock, circulatory failure, and a fatal termination may ensue.

Constitutional reactions are encountered most frequently in connection with the treatment of hay fever. Hence it is important to keep in mind the possibility of their occurrence and to be careful of the dosage employed either for treatment or for testing. It is also well to keep the patient under observation for 30 minutes following treatment in order to be able to institute immediate measures if neces-

sary. The treatment of a constitutional reaction is as follows: the tourniquet is placed above the point of injection on the arm in order to delay absorption. Epinephine hydrochloride (1-1,000 solution) is given subcutaneously in the other arm in a dose of 0.5 to 1 cc. repeated in 15 minutes, depending on the severity of the reaction. In extremely severe cases this medication may be given intravenously. Ephedrine sulfate gr. 3/8 to gr. 1/2 may be prescribed. Where nervous manifestations are marked, sedatives or very small doses of opiates may be necessary. Even under the best controlled conditions, constitutional reactions are occasionally encountered. However, the reaction is usually checked easily if the treatment is instituted promptly (for equipment see Fig. 16).

DISCUSSION ON ALLERGENS

The great number of substances which may cause allergic manifestations as well as the variety of forms in which these allergens may be found make it necessary for the allergist to have an intimate acquaintance with the subject. There are many sources from which this special information can be obtained. Among these, one of the most valuable is the chapter on "Allergens" by Katherine Bowman in the book by Coca, Walzer, and Thommen* titled Hay Fever and Asthma.

The following is included to give the reader some idea as to the various forms in which some of the more common allergens are found.

Inhalants. Pollens. These are important inhalant allergens which will be discussed in the chapter on hay fever—Chapter 6.

Animal Danders. Danders are very potent allergens and give rise to many forms of allergic manifestations of the

* Springfield, Ill., Charles C Thomas, Publisher, 1931.

skin and respiratory tract. Frequent constitutional reactions may be obtained from exposure to these allergens (testing, etc.). There seems to be an interrelationship between sensitivity to *horse dander* and *horse serum*. Practically all per-



Fig. 16. Tray with supplies for treatment of constitutional reactions

sons who are sensitive to horse serum are also sensitive to horse dander. The reverse is not always true Contact with horses, especially riding behind a horse or coming in contact with horse blankets or other riding habit, may produce severe symptoms of asthma.

Cat dander is significant from a clinical standpoint because symptoms may result from contact with cats or from playing with certain toy animals stuffed with cat hair, or from wearing cat furs.

Dog epithelium is a common allergen because of the frequency of these pets in the home.

Goat epithelium may be found in certain types of bedding, in rugs, blankets, cushions, mohair, and so-called camel's hair fabrics.

Rabbit hair is found in stuffed toys, silk, felt hats, furs (so-called ermine), stuffing in cushions, mattresses, and pillows.

Sheep wool is used in the manufacture of clothing, felt hats, doll's hair, and slippers

As for *feathers*, the active principle in the extract of feathers is not exactly clear. It does not seem that there is a specific and different atopen in *chicken, duck, or goose epithelium*, and for this reason an extract of a mixture of the three epithelia is usually employed in testing. It has been suggested that there is a more potent active principle in old than in fresh feathers, and that this increased activity is due to contamination of old feathers with molds.

Orris Root This is a potent allergen. It is found in most cosmetics, face powders, and tooth pastes Certain advertised tooth pastes are free of orris root. It produces symptoms either because the patient uses it himself or because he comes in contact with other individuals who use orris-root-containing cosmetics It is sometimes used in the preparation of adhesive plaster and occasionally in the manufacture of gin

House Dust This is probably the most important inhalant allergen, containing a common "x" substance thought to be the active principle. Just what this "x" substance represents is not exactly known It seems likely that it is not merely a combination of all the inhalant allergens and dusts to which the patient is exposed There is some evidence that it contains the active principle of cotton linters Nasal and pulmonary allergy is frequently due to house dust The extract is prepared in accordance with

principles stated elsewhere in this chapter. More recently there has been a report of a new method of concentrating house-dust allergen by subjecting aqueous extracts of house dust to two successive fractional precipitations with dioxane (diethylene oxide). The resulting product is said to be more potent than the dust extract prepared by the conventional method.

PYRETHRUM. Most insecticides formerly contained pyrethrum, unavailable at the present time due to the war. Pyrethrum-sensitive patients may use certain pyrethrum-free products such as "Kilit" (National Allergic Sales Co., New York City) or Lethane 384 (Rohm and Haas Co, Philadelphia).

INSECT EMANATIONS. Allergy by inhalation of the emanations of sandflies and various other insects is a serious clinical problem in the region of the Great Lakes and in many other parts of the country. Of these insects the May fly and the sandfly are the most frequent offenders. Sensitivity may be demonstrated by skin testing with suitably prepared extracts Allergy to bedbugs has been responsible for some reported instances of asthma.

Foods. EGGS Egg acts almost entirely as an ingestant but it is rather an important one, especially in infants and children. Allergy to eggs may lead to skin manifestations, respiratory allergy, or gastro-intestinal symptoms. A strong positive skin reaction to egg extract as a rule has clinical significance. It is thought that sensitivity to egg yolk independent of sensitivity to egg white is practically impossible. It would also appear that there is a close relationship between the antigenic nature of hen and duck eggs, so that substitution of one type of egg for another is not practical. Sensitivity to chicken eggs as a rule carries with it sensitivity to chicken meat, although this is not always the case. There are times when it is desirable to test a patient with various fractions of eggs such as the ovomucoid, the albu-

men, and the globulin fraction Occasionally, heating eggs to boiling will make it possible for the patient to eat them provided he is not sensitive to the ovomucoid fraction, as the latter is not coagulated or altered by heat.

Eggs are found, of course, in a variety of foods. They are used in cooking various dishes, as well as in baking. To mention only a few products, mayonnaise, macaroons, bread, waffles, cakes, muffins, ice creams, meringues, icings, covering for bonbons, and certain sauces such as Hollandaise contain eggs. Eggs are also used for giving a glazed appearance to the crust of bread, for preparing sausages and beef juices, and occasionally for the manufacture of baking powder.

MILK. The albumen fraction of milk seems to be the most important antigenically, and for this reason a milk-sensitive patient may occasionally drink milk that has been boiled for 15 or 20 minutes. In those instances where cow milk is not tolerated it is frequently possible to substitute goat milk or other preparations such as soy bean, almond, or poppyseed milk. These products are available in cans. Coexisting sensitivity to cow milk and beef is not so frequent as that between eggs and chicken meat. Milk is found in a variety of foods such as custard, bread, candy, *etc.* Cheese is, of course, prepared from casein, the principal protein of milk, and it may contain small quantities of albumen Milk is found on the market in various forms. Condensed milk is sugar-containing milk from which a considerabl[illegible]
milk i[illegible]
and p[illegible] milk has all its water removed. During the removal of the water, in most instances, the milk is heated to a fairly high temperature. For this reason, some evaporated milk may be tolerated by individuals who are sensitive to fresh milk Certain cheeses made from milk other than cow milk—as for example Roquefort cheese from

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instances have appeared where an individual sensitive to cod could not take cod-liver oil, but these instances are rare.

MEATS. The active principle in meat is probably a protein Cooking, in many instances, unquestionably seems to reduce the potency of meat as an allergen. Occasionally a patient may be very strongly allergic to such meat as chicken meat and develop severe urticaria or allergic headaches

NUTS Nuts are potent allergens. Frequent constitutional reactions may be induced as the result of even intradermal testing with usual dilutions The ingestion of nuts may cause asthma, and in some instances allergic headaches. Nuts are widely used in the preparation of such foods as candies and confections They may be found in various cereal drinks such as nut milk and nut paste, preserves, fritters, and candied nuts Nut meals and flours are used for making bread Where sensitivity does occur to any nut, it is usually specific for that nut alone and as a rule is very marked, so that even the smallest quantity of it when found in some disguised form in any food may produce severe symptoms Even the oils from nuts may contain a sufficient amount of protein to be allergenic. Examples of this may be found in peanut oil-sensitive cases where the individual develops a constitutional reaction from the administration of epinephrine in peanut oil.

Almonds in the form of *almond oil* are found in many cosmetics Sweet almond oil is frequently substituted for olive oil

Cocoanut oil is also used in the preparation of foods and cosmetics

Peanuts are used extensively as food They may also be eaten *roasted* or in the form of *candies* or peanut butter Peanut oil may be used as a substitute for olive oil in the manufacture of oleomargarine or for packing olives or sardines

sheep's milk, Lipton cheese from goat's milk, etc.—find a place in the diet of certain patients.

CEREALS. Cereals constitute a major portion of our foods and are important allergens or atopens because they may produce symptoms not only as a result of ingestion but also as a result of inhalation and contact. Under the heading of cereals are included wheat, buckwheat, corn, rice, rye, oats, and barley. Of these perhaps the most important is wheat.

Wheat. Coffee substitutes are made of wheat and other cereals. Postum is an example of this. Wheat flour is used in baking breads, batter, crackers, sauces, macaroni, spaghetti, noodles, and various other products. Wheat is also used in the preparation of certain toilet powders. The list of cereals containing wheat is almost endless. Some people may develop eczema or asthma as a result of ingestion of wheat or wheat-containing foods. Others (bakers, for example) may develop a dermatitis from coming in contact with wheat flour. Still others may develop asthma without any dermatitis as a result of inhalation of flour.

Corn. Corn is found in the various breakfast cereals. It is also used in the preparation of beer and whiskey. It may be found in cornbread, corn mush or corn muffins. Corn or maize oil is used as a salad oil.

Rice. Rice is found in breakfast foods, may be used as a vegetable or in soups, or it may be made into a flour. In the latter form it may enter into the manufacture of toilet powders.

Rye. Rye goes into the preparation of breakfast foods, whiskey, and bread.

FISH. Fish is a common offender in allergy, frequently yielding constitutional reactions. Many people have an idiosyncrasy to the odor of cooked fish, and others will get an attack of asthma when exposed to such odors. Still others get urticaria and angioneurotic edema from eating fish. The active allergen as a rule is a protein, although some

Flaxseed may act as an allergen either by inhalation or ingestion.

Linseed oil is made from flaxseed and is used in the preparation of furniture polish, linoleum, oilcloths, and varnishes. It is also found in hair tonics.

Kapok seed is occasionally of some importance in the production of allergic manifestation.

Miscellaneous Allergens. KARAYA OR INDIAN GUM. This has found a variety of uses. For this reason, it is essential to test patients suspected of possible sensitivity to this substance. Karaya gum may be found in ice creams, gum drops, tooth pastes, diabetic foods, some junkets and gelatin preparations, hand lotions, permanent-wave sets, laxatives, mineral-oil products, dental powders, candies, etc. Wave-setting fluids contain Karaya gum, tragacanth, flaxseed, or quince seed. For this reason proper testing is indicated in suspected allergic patients before determining which preparation is safe in a given case.

SUMMARY

The allergic survey includes first the establishment of the likelihood that the patient's condition is allergic by eliciting *the criteria* for allergic diagnosis. These are heredity, associated allergic manifestations, eosinophilia, positive skin tests, response to epinephrine, and development of symptoms on clinical exposure.

Diagnostic methods in the study of the allergic patient include a carefully taken *history*, physical examination, diagnostic or sensitization *tests*, and *laboratory* and special examinations. The diagnostic or sensitization tests include skin tests such as the scratch test, intradermal, patch, and the passive transfer or indirect tests. They also include ophthalmic, nasal, and elimination tests. The laboratory examinations include examinations of the *urine*, the *blood* (blood count), and serology, the sputum for tubercle bacil-

VEGETABLES AND FRUITS. Vegetables and fruits are frequent offenders in allergy. It has been shown that a patient's skin will frequently react to the juice of a fresh vegetable or fruit and not to a carefully prepared extract of this food. There are many factors which must be taken into consideration in the preparation of these extracts. It is generally known that they are notoriously unstable and frequently yield nonspecific reactions. Sensitivity may be manifested to the fruit juice or to the rind.

SPICES AND CONDIMENTS. Spices and condiments may produce serious allergic manifestations, although their importance is not usually recognized. They may be employed in cooking or in the preparation of beverages or flavors. They may affect the patient as a result of ingestion or inhalation Mustard is an example of this group. It produces symptoms by direct local application such as in mustard plasters or as a food. Sensitivity to oil of peppermint or oil of wintergreen as a rule is very marked. The writer has obtained a constitutional reaction by allowing a patient sensitive to oil of wintergreen to taste with the tip of his tongue an applicator which had been dipped in a solution of oil of wintergreen. This patient presented a history of asthma after eating certain types of hard candy which later were found to contain oil of wintergreen.

SEEDS. Allergy to *cottonseed* expresses itself in respiratory symptoms. There is serious doubt as to whether the ingestion of cottonseed oil may give rise to allergic symptoms, although this is probable in patients who are extremely sensitive to cottonseed In these instances the sensitivity must be to a water-soluble fraction of cottonseed One should keep in mind the possibility that cottonseed flour is used in the preparation of certain foods, and that cottonseed oil is used in mayonnaise and in packing sardines and other foods.

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lus, the *examination of nasal secretions, and leukopenic* index. Special examinations should include, when indicated, a roentgenogram of the chest, an electrocardiogram, the determination of vital capacity, nose and throat and dermatologic consultations.

There are numerous methods of preparing extracts for the testing and treatment of allergic patients. The steps involved in their preparation aim to extract from the product the largest amount of active principle. The ideal extract is one which is biologically potent and specific, and *which will retain its potency for a long period of time* Extracts are standardized either by their nitrogen content or by the dilution method. Occasionally it is necessary to prepare autogenous extracts. A certain minimum amount of equipment (syringes, needles, and extracts) is necessary for carrying out an allergic survey

Constitutional reactions may result during the course of testing or treatment of an allergic patient Prompt and adequate treatment of these reactions is essential An intimate knowledge of the possible sources of various allergens is *also of value in the proper diagnosis and management of* allergy.

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5

Treatment of Allergy

BROAD CONSIDERATIONS
GENERAL THERAPEUTIC MEASURES
CASE REPORTS
AVOIDANCE OF CAUSATIVE FACTORS
"DESENSITIZATION"
MEDICINAL TREATMENT
DIET THERAPY
SUMMARY

BROAD CONSIDERATIONS

It is necessary to emphasize that the treatment of an allergic condition is, as a rule, a painstaking and prolonged procedure. Unfortunately, the opinion is still prevalent in some quarters that allergic management involves only the performance of a series of skin tests followed by avoidance of contact with and exposure to those substances to which skin reactions are positive Thereupon it is expected that the patient will improve promptly. This attitude only too often has led to disappointment and discouragement and has brought about a great deal of skepticism on the part of the profession with regard to the efficacy of allergic procedures As a matter of fact, the problem is not quite so simple Skin tests are not always reliable and are not uniformly accurate in the hands of different workers Clinical observation of the patient is far more important for diagnostic purposes and not infrequently leads to the discovery of factors of therapeutic importance

It is obvious, therefore, that satisfactory management of the allergic patient really begins upon the completion of

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tomy should be made as though the patient did not have allergy The same therapeutic approach should govern the decision of removal of other foci of infection such as infected teeth and the treatment of infection in the paranasal sinuses

Correction of Coexisting Pathology. Gastro-intestinal disorders, secondary anemia, and other conditions must be properly treated

Psychotherapy and Psychosomatic Approach. An understanding of the relation of allergy to the nervous system and to the behavior pattern of the individual is essential in proper psychotherapy.

It has been shown in Chapter 3 that preponderance of that part of the autonomic nervous system known as the parasympathetic (vagus) brings about certain functional changes such as smooth muscle spasm, low blood pressure, etc —changes characteristic of allergy. In some instances allergic manifestations seem to be induced as a conditioned reflex, on the other hand, there are some which may directly affect the nervous system These are Ménière's syndrome, allergic headaches, migraine, angioneurotic edema, and some forms of infantile convulsions.

Still another phase of the relation of allergy to the nervous system includes (1) the influence of allergic disorders on the emotional make-up of the patient, and (2) the effect of emotional conflicts on the development and course of the allergic disorder

The patient who has been subject to repeated and frequent asthmatic paroxysms or to continuous pruritus from an allergic dermatitis naturally becomes irritable and discouraged The intensity of his emotional reaction, and even his ability to function as a normal individual, depend on the gravity and duration of the allergic disorder If the disorder began in childhood the influences on the child's personality may be very marked The child becomes in-

an allergic survey. It is at this time that the patient is acquainted with the fact that the very nature and duration of his condition necessitate observation and treatment over a long period of time. An effort is made to provide him with some suitable literature on allergy to arouse his interest in order that he may become more observant and more cooperative.

In view of the fact that the general principles of allergic treatment are practically identical in various allergic disorders, it is advisable to discuss them together in this chapter and subsequently to take up special forms of therapy as *they apply to individual allergic diseases*

GENERAL THERAPEUTIC MEASURES

Prophylaxis. The prevention of allergic diseases includes avoidance on the part of allergic individual of exposure to substances which may produce symptoms. In spite of the fact that some allergic disorders are familial, we do not believe that marriage between two allergic patients is contraindicated The early and adequate allergic treatment of allergic children is an effective prophylactic measure Modern hygienic measures provided in large industrial establishments (ventilation, bathing, protective clothing, etc.) are also effective prophylactic measures.

Elimination. Proper attention must be paid to elimination.

Rest. The patient must obtain sufficient rest and relaxation.

Removal of Foci of Infection. Foci of infection are removed when present, not because it is expected that the procedure will cure the allergic condition, but because their removal may contribute toward improving the general health of the patient. Removal of diseased tonsils, for example, does not have a specific effect on the allergic condition. The decision as to whether to perform a tonsil-

tional difficulties produce allergic symptoms, but rather that such conflicts will influence the clinical course and prognosis of an existing allergic condition. For these reasons it is essential to include adequate psychotherapeutic measures in the treatment of allergy. In days past such measures came under the heading of the art of medicine as practiced from time immemorial by the family physician, who, because of his intimate acquaintance with his patients and their families, knows a great deal about their problems. He is frequently in a position to see the relation between a patient's background, his emotional upsets and conflicts, and the symptoms of which he complains. Through such an understanding the wise physician in many instances can trace the effect of these influences on the patient's health.

With increased specialization and increasing emphasis on organic pathology, this phase of medical practice is suffering, and it is only recently that we have rediscovered it under a more euphonious term—namely, psychosomatic medicine. We have again become aware that an individual who is maladjusted cannot be well and happy, and that psychogenic disturbances and behavior patterns may either aggravate already existing symptoms or in many instances produce these symptoms We are realizing that, in spite of a correct diagnosis and adequate objective treatment, an occasional patient does not improve because the treatment which he receives does not include attention to his emotional make-up and behavior difficulties. Numerous examples of the effect of maladjustment on the appearance of the allergic paroxysm could be cited

CASE REPORTS

CASE 1 Patient, female, aged 23, had had asthma, hay fever, and occasional eczema since the age of nine. Her allergy was definitely of the *extrinsic* type She was sensitive to many inhalants, to pollen, and to some foods Her con-

troverted, submissive, and may lead the life of a cripple, demanding a great deal of sympathy and attention and refusing to partake of his normal responsibilities. Or he may overcompensate and become extroverted and aggressive Even more serious psychic disturbances may develop in the unbalanced and constitutionally inadequate, requiring special neuropsychiatric care.

Emotional upheavals, on the other hand, unquestionably have an important bearing on the bodily function of any individual, and in many instances particularly influence the character, frequency, and severity of the allergic paroxysms. Every internist has seen patients who develop severe attacks of asthma when under severe emotional strain, or a patient suffering from atopic dermatitis whose dermatosis flares up under similar circumstances Under the impact of anxiety, fear, or some other emotional explosion, the cough, dyspnea, or pruritus becomes unbearable. The patient's irritability increases, he becomes sleepless, loses his appetite and weight, and becomes very ill. With improvement in his psychogenic disturbance, allergic treatment becomes more effective. That emotions can affect normal body functions is obvious. Such acts as blushing, palpitation, nausea, vomiting, pallor, diarrhea, sweating, insomnia, etc, are physiologic phenomena influenced directly by the emotional state of the individual. They are normally reversible. There are some individuals, however, who develop a state of chronic intense emotional strain as a result of continuous conflicts of one type or another. In these patients the emotions do not find an outlet, their repressive drives lead to maladjustment, and this state in turn affects deeply the clinical manifestations of allergy whether referable to the nose, the lungs, or the skin. This group of patients is frequently refractory to medical treatment and presents grave therapeutic problems

It is not intended to convey the impression that emo-

Arizona. In spite of this, he continued to get asthmatic attacks which were quite severe and which did not always respond to the administration of adrenalin. His condition was such that, because of the fear of a possible attack of

condition seemed entirely too refractory to treatment. The occurrence of the attacks was erratic. Certainly the episodes for which he had to be hospitalized were in no sense similar to what is recognized as status asthmaticus. It was obvious that, because of these facts and also because of the absence of any contributory conditions such as nasal infection or pulmonary pathology, there must have been some other component in this clinical picture. For these reasons he was referred for psychotherapy. An effort was made to obtain information pertaining to the life history of this boy, with the following results.

While in high school, in spite of his asthmatic condition, his drive was sufficient to enable him to be *quite active* in athletics and even to play football. He wanted to continue his studies, and his life ambition was to attend college and become an engineer. In this ambition he was thwarted by his physical condition and by lack of funds. *In discussing* this disappointment he pointed out that he had never

to understand him) than to his father, who was quiet and talked very *little*. The boy had to support his family and had been contributing 50 *per cent of his earnings although* he thought he should be allowed to keep it. He had been classified as 4F and was hurt about *it*. *He felt* himself to be "as good as the next *one*" *were it not* for his asthma. He was becoming extremely irritated with his condition, finding himself alone during the day, when he did not feel well, and seeing his friends *only in the* evenings. He was very hurt about being classified as 4F and his chief concern was to get a job *in* a shipyard where he could help in the war effort.

dition showed improvement with treatment. She was an intelligent, high-strung young lady, very unstable emotionally. Her home surroundings placed her in constant emotional conflict. Her interest in a young man made her panicky with fear and anxiety lest her allergic condition interfere with the prospects of marriage. The chronic tension aggravated the skin condition so that she developed a severe generalized atopic dermatitis which resisted all forms of treatment. Psychotherapy was employed extensively in conjunction with allergic management. As a result of these procedures the patient found it possible to effect a more normal emotional adjustment. Following her marriage the dermatitis improved quite promptly.

CASE 2. Patient, female, aged 52, a widow, had had some "bronchitis" for many years. She began to be troubled with constant, severe, and frequent paroxysms of asthma. She was sleepless, her appetite was poor, and she lost weight. Investigation revealed not only the presence of definite allergic factors but also the information that her best friend had died shortly before the onset of her condition, and that her niece, who was very close to her, had married and moved out of town. She found herself suddenly alone, without any close friends or relatives, and became introspective, sad, and anxious about her future. With proper psychotherapy, in addition to general medical and allergic treatment, her condition improved.

CASE 3. Patient, male, aged 20, also illustrates the role of psychosomatic influences on the course of a patient's clinical allergy. This young man presented a history of seasonal hay fever and bronchial asthma which began while he was in high school, six years previously. There was a strong positive family history of asthma. There was also blood eosinophilia. The skin tests corroborated the presence of pollen allergy and of sensitivity to other substances. The nose showed evidence of numerous polyps which had been removed from time to time. There was no evidence of suppuration in the nose, nor was there any sign of other pathology.

The patient had received adequate medical and allergic treatment from the beginning of his condition. This included proper dietetic therapy, pollen and house-dust treatment, medicinal therapy, and even a change of climate to

vironment and in his diet occur in a disguised form, so that he is inadvertently exposed to them.

For this reason, it is frequently necessary to make a complete survey of the patient's home, his business environment, and his habits. It is surprising how often even the most intelligent patient, despite careful questioning, fails to think of matters with which he should be familiar. To cite but two examples: a young woman who gave a history of asthma was found sensitive to horse dander. An excellent rider, she had to give up horses because she would develop asthma when near them. Warned repeatedly about the nature of her sensitivity, her asthmatic paroxysms, however, continued almost every night. Subsequent investigation revealed the fact that, for lack of storage space, she kept the saddle and horse blankets under her bed.

Another patient, a gin mixer in a distillery, had a very severe allergic rhinitis. He was found sensitive to orris root, among other things. Orris root is a common ingredient of various cosmetics, shampoos, and toothpastes. He was warned about his orris-root sensitivity. However, in spite of treatment, his symptoms continued. Six weeks following the institution of allergic treatment, further detailed questioning revealed the valuable information that in the mixing of gin he threw about a handful of orris root into the vat. It was only after the significance of this fact was pointed out to him that he realized that he sneezed a great deal more when at work than at other times.

Preparation and Maintenance of a Dust-free Room. In order to avoid house dust, an allergen of particular importance in respiratory allergy, the patient is given a list of directions which will help him as much as possible in ridding his house of dust. A suggested set of directions follows.

It is desirable to render the patient's bedroom dust-free. It should be entered seldom by others. Cleaning should be

The attending psychiatrist, in analyzing the above life situation, stated: "The boy is concentrating on his somatic symptoms. He has expressed doubts as to whether there is any emotional factor as he sees it. There is no evident anxiety and this is only natural because of the obvious physical symptoms. The boy expresses some irritation and hostility toward his younger brother whom he discusses as an equal rather than as a boy ten years his junior. He is quite evidently aware of the fact that this brother does control much of his parents' feelings, and he resents the attention shown him. Although he insists that everything is all right at home there is strong evidence of open rebellion against his parents which is expressed in feelings of guilt during the asthma attacks For example, desire to work is primarily to bridge his feelings of difference in relation to the other boys of his own age and also to become self-sufficient and no longer dependent upon his parents."

This history is presented in order to indicate the necessity of psychotherapy in a certain group of allergic individuals. Such treatment must be part of the general allergic and medical attention which the patient receives, and in many instances it will determine the clinical outcome of the case.

AVOIDANCE OF CAUSATIVE FACTORS

In many allergic disorders, particularly those in which symptoms are due to a single factor, the first and most important step in treatment is to avoid completely any exposure to the offending agent. When the nature of this single agent is known, the procedure is usually not difficult. But most instances of allergy are due to multiple rather than single sensitization, and in these cases the problem of avoidance is not a simple one. This is due to the fact that so many of the allergens present in the patient's en-

and toothpastes Those who are sensitive to feathers must procure dust-proof pillow slips Mattress covers are prescribed in instances of allergy to cotton or horsehair. Avoidance of contact with animals involves disposing of one's favorite pet dog or cat. Frequently, however, there is enough animal dander on the furniture to continue to cause symptoms long after the animal has gone. Animal hairs occur in toys, felt hats, door mats, and furs. The commercial name of a fur does not always indicate the source of the fur Thus, dyed muskrat becomes mink or sable; pulled and dyed muskrat sells as seal or Hudson Bay seal, dyed hare is marketed as sable fox, and white rabbit is sold as ermine

Avoidance of Offending Foods. Individuals sensitive to certain foods must avoid them in whatever form they may appear Thus, sensitivity to wheat involves avoidance of many foods which ordinarily are not known to contain wheat Similarly, allergy to egg indicates the necessity of avoiding egg-containing foods These include cakes, muffins, noodles, ovaltine, beef juices, mayonnaise, ice cream, glazed candies, custards, and many other foods Milk may be found in bread, cake, ice cream, cream sauce, noodles, malted *milk*, macaroni, dryco, and other foods. It is well to give some form of calcium to the patient who eliminates milk from his diet In infants, goat or human milk may be substituted for cow milk. Cooking destroys by coagulation the *active principle* in many protein foods, and for this reason milk- and egg-sensitive patients may eat hard-boiled eggs and [illegible]

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[illegible] to the essential oil in the rind should be kept in mind, and in such *instances* the orange juice should be squeezed by hand One must be careful, however, to prevent the development of deficiency diseases when restricting the diets of allergic patients Some time ago an asthmatic patient reported to the University Clinic for treat-

done only when the patient is out of the room. Remove all hangings, carpets, and extra furnishings from the sleeping room, as they are dust catchers. There should be no overstuffed (upholstered) furniture in the room. Clean the walls and ceilings. Scrub the woodwork (floors, baseboards, closets, etc.), scrubbing should be repeated each week. Scrub the bedsteads and all open coil springs at least once each month. A scrubbed wooden or metal chair may be used. Use cotton rag rugs and plain light curtains, and wash them weekly. Window shades (blinds) of the pull type are desirable. It is most important that mattresses, pillows, and upholstered box springs be enclosed in dust-proof covers Use only washable blankets and washable cotton bedspreads (use no chenille or tufted candlewick type); blankets should be washed at least once each month. (For woolen blankets this washing may be done in the bathtub in a simple manner. The use of "Dreft" suds is recommended, as they remove fiber dusts rapidly). If there is sensitivity to wool, ordinary cotton blankets may be put into sheets (old, soft, well laundered) before being brought into the room. These sheets should be changed only outside the room.

Do not store household objects or outer clothing such as shoes and overcoats in the clothes' closets. When possible, the ventilation is to be obtained from outdoors. A suitable ventilator with a filter should be installed in the window. All doors leading to other rooms should be kept closed. If furnace heat outlets exist, a dust filter must be installed and changed frequently.

Avoidance of Other Offending Inhalants. Other common offending inhalants are orris root, feathers, animal danders, tobacco, wool, silk, glue, flaxseed, and pollen. A detailed account of the various forms in which these allergens may be met is to be found in Chapter 4. Sensitivity to orris root involves a change to non-orris-containing cosmetics, soaps,

Meats

All meats may be eaten if prepared without wheat or wheat products Ready-prepared meats such as cervelat, frankfurters, hamburger, meat loaf, and sausage frequently contain wheat products as fillers.

Milk and Dairy Products

Butter, buttermilk, cheese, cream, evaporated milk, ices, ice cream, sherbets, whole or skimmed milk.

Miscellaneous

Popcorn, potato chips, raisins, and salad dressings if made at home without the addition of wheat products Nuts, olives, and pickles

Poultry and Game

Use no wheat products in preparation.

Soups

Homemade vegetable, cream, or meat soups (Heinz cream soups, except cream of mushroom, contain no wheat)

Sugars

Brown, granulated, powdered, confectioner's, and maple Homemade jellies, jams, preserves, and candies

Vegetables

All kinds, raw, canned or cooked Add only butter, milk, cream, or eggs in preparation Do not combine with wheat products

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Forbidden Foods

Beverages

Cereal beverages or coffee substitutes made from wheat (Information as to ingredients may be found on can or package) Malted drinks, beer or ale

Breads

Hot bread such as muffins, popovers, baking powder biscuits made with wheat products, griddle cakes, waffles, or doughnuts Wheat breads, crackers (except Ry Krisp) Gluten bread, graham bread, pretzels, cornbread or rye bread (unless made at home without wheat flour), white bread, whole-wheat bread, bread stuffing, or Zwieback

Breaded Foods

In which the breading mixture contains wheat.

Cereals

All dry or cooked cereals made from or containing whole wheat, farina, or bran

Desserts and Pastries

Cakes, cookies, custards (unless thickened with eggs or

ment. She was food-sensitive, and restriction of her diet brought about considerable improvement. As is the usual routine of the clinic, this woman was instructed to report back at periodic intervals in order to make additions to her diet and prescribe whatever minerals and vitamins were necessary. She not only failed to return, but restricted her diet still further, with the result that about eight months later she was admitted to the hospital with pellagra.

Wheat, milk, and eggs are the most common food allergens. For this reason, wheat-free, milk-free, and egg-free diets may have to be given to allergic patients Samples of each are included (see Tables 6 to 13).

TABLE 6

WHEAT-FREE DIET *

Allowed Foods

Beverages
Cocoa, coffee, fresh or bottled fruit juices, mineral or carbonated waters, tea.

Breads
Ry-Krisp, cornbread, oatmeal or potato muffins made without wheat Use only recipes recommended by physician

Breaded Foods
In which the breading mixture contains no wheat (Ry-Krisp crumbs may be used for breading)

Cereals
Barley, barley flour, cornflakes, cornmeal, cornstarch, potato flour, rice flour, rice flakes, rolled oats, rye, tapioca. Ry-Krisp wafers crumbled and served with cream and sugar *may be used as breakfast cereal*

Desserts
Bavarian cream, cornstarch pudding, fruit gelatins, homemade *ices or ice cream,* oatmeal, rice, or rye cookies, tapioca pudding, Indian pudding, Ry-Krisp Crumb Crust.

Fruits
All kinds, raw, canned or plain, cooked with sugar, honey, or syrup

* Courtesy, Ralston Purina Co, St Louis, Mo

Desserts

Fruit gelatins, pudding, shortcakes or cookies made without dairy products Fruit ices made with water Do not use prepared mixes or powders

Egg Dishes

Prepared without milk, butter, or cream.

Fats

Poultry, vegetables, or meat fats, olive oil or other salad oils Oleomargarine, if not churned in milk

Fruits

All kinds, raw, canned or plain cooked with sugar, honey, or syrup—served without milk or cream

Meats

All kinds prepared without dairy products

Miscellaneous

Potato chips or popcorn prepared without butter, raisins, nuts, olives, pickles

Pastries

Cakes, cookies, and pie crusts made according to recipes recommended by your physician.

Salad Dressing

French dressing, mayonnaise, or other salad dressings made without dairy products.

Sea Foods

All kinds Use no dairy products in preparation.

Soups

Meat or vegetable soups made at home without dairy products

Sugars

Brown, granulated, powdered, confectioner's, and maple Homemade jellies, jams, and preserves

Vegetables

All kinds, canned, cooked, or raw, prepared without butter, milk, cheese, or cream

Forbidden Foods

Beverages

Chocolate or cocoa unless made with water (Avoid prepared cocoa powder made with dried milk) Malted milk, or any prepared drink made with milk

Breads

Hot breads such as muffins, popovers, baking powder biscuits, griddle cakes, pancakes, waffles, or doughnuts unless prepared without milk or other dairy products Whole-wheat

cornstarch), doughnuts, dumplings, puddings, pie, pastries, and ice cream cones

Meats

Ready-prepared meats, such as cervelat, hamburger, frankfurters, or sausage which may contain wheat as a filler. Croquettes, fish rolled in cracker meal or crumbs, and meat loaf Swiss steak, wiener schnitzel.

Miscellaneous

Gravies, griddle cakes, malt products, waffles, yeast, pretzels, chili con carne, spaghetti, vermicelli, macaroni, or saltines. Prepared mixes for biscuits, cakes, cookies, doughnuts, muffins, or pie crust.

Sauces

Butter sauce, cream sauce, or white sauce if wheat is used for thickening.

Soups

Cream, chowder, vegetable, noodle, or meat soups unless prepared at home without wheat.

Vegetables

Baked beans unless prepared at home without wheat Any vegetables served with a sauce made with wheat flour

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TABLE 7

MILK-FREE DIET *

Allowed Foods †

Beverages

Cocoa made with water from milk-free chocolate or cocoa Coffee or tea, without milk or cream Fresh or bottled fruit juices, mineral or carbonated waters.

Breads

Ry-Krisp, cornpone, wheat, rice, rye, graham, and gluten breads in which no dairy products are used.

Candies

Made at home without milk, butter, or cream.

Cereals

All kinds, served without milk or cream

* Courtesy, Ralston Purina Co, St Louis, Mo

† Evaporated milk may, in many instances, be included in the diet of persons sensitive to the whey protein of raw or pasteurized milk. Ask your doctor about this

TABLE 8

EGG-FREE DIET *

Allowed Foods

Beverages
Cocoa, coffee, fresh or bottled fruit juices, mineral or carbonated waters, tea

Breads
Ry-Krisp, cornpone, wheat breads Rye or rice breads made from an egg free recipe Most commercial breads have eggs as an ingredient, or are brushed with egg white to glaze the top

Cereals
Whole-wheat cereals, barley, barley flour, cornflakes, cornmeal, cornstarch, potato flour, rice flakes, rolled oats, rye or tapioca, Ralston Wheat Cereal, Shredded Ralston

Desserts
Fruit gelatins, cookies, frostings, cake or pudding-made without eggs Use only recipes recommended by physician

Fats
Butter, meat, poultry or vegetable fats olive oil, oleomargarine

Fruits
All kinds, raw, canned, or plain, cooked with sugar, honey, or syrup.

Meats
All kinds, prepared without eggs

Milk and Dairy Products
Butter, buttermilk, cheese, cream, evaporated, condensed or dried milk, whole or skimmed milk.

Miscellaneous
Popcorn, potato chips, raisins, nuts, olives, pickles.

Pastries
Use only recipes recommended by physician or those given on reverse side of sheet Royal baking powder does not contain egg

Poultry and Game
Use no egg products in preparation

Salad Dressings
Made at home without the use of eggs

Sea Foods
All kinds Use no eggs in preparation.

* Courtesy, Ralston Purina Co, St Louis, Mo

bread, white bread, gluten, rye, or graham bread unless prepared without milk or other dairy products Zwieback.

Candies

All candies, unless homemade without dairy products or ingredients containing dairy products

Dairy Products

Butter, buttermilk, condensed or dried milk Cream, curd, ice cream, and sherbets Whole or skimmed milk Powdered or malted milk. Whey. All cheeses.

Desserts

Bavarian cream, blanc mange, cakes and cookies made with milk, cream or butter. Custards, ice cream, milk or cream sherbets Pie crusts made with butter Puddings made with dairy products Spanish cream.

Dishes Prepared with Milk

Boiled salad dressing unless homemade without dairy products Creamed foods, foods fried in butter, escalloped dishes, foods prepared au gratin Gravies made with milk, cream, butter, or other dairy products. Omelets or scrambled eggs prepared with milk, cream, or butter. Rarebits, soufflés, or timbales.

Meats

Frankfurters or any processed meat to which dried skim milk has been added Wiener schnitzel

Miscellaneous

Fritters Oleomargarine, if churned in milk. Popcorn, unless prepared at home without butter Milk chocolate. Prepared mixes for biscuits, cakes, cookies, doughnuts, muffins, pie crust, or waffles.

Sauces

Milk or cream sauces such as white sauce, butter sauce, or hard sauce.

Soups

Bisques and chowders, unless homemade with water All cream or milk soups.

Vegetables

With butter, milk, cheese, cream, or white sauce

Miscellaneous

Griddle cakes, dumplings, pretzels, noodles, marshmallows, soufflé, French toast, fritters, prepared mixes for biscuits, cakes, cookies, doughnuts, muffins, or pie crust.

Pastries

Macaroons, meringues, or pies (such as custard, lemon, coconut, and pumpkin) Puddings, unless homemade without eggs Spanish cream, timbales, waffles

Salad Dressings

All salad dressings unless homemade without eggs

Sauces

Hollandaise sauce, Tartar sauce, mayonnaise.

Soups

Mock Turtle, consommé, bouillon, noodle, or any soup made with egg or from ingredients containing egg

TABLE 9

THE WHEAT, EGG, AND MILK-FREE DIET *

If You Are Sensitive to Wheat, Eggs, and Milk, You May Eat the Following Foods.

These foods must be prepared without the use of wheat products, eggs, and dairy products

Beverages

Cocoa made with water, coffee or tea without cream or milk fresh or bottled fruit juices, mineral or carbonated waters

Breads

Without wheat, eggs, or milk, cornbread or cornpone, rice, Ry Krisp, or whole rye (Use recipes found in Table 13, or those prescribed by your physician)

Candies

Made without dairy products, such as fondant, molasses taffy, French paste

Cereals

Barley, barley flour, cornflakes, cornmeal, cornstarch, potato flour, rice, rice flakes, rolled oats, rye, tapioca, crumbled Ry-Krisp wafers

* Courtesy Ralston Purina Co, St Louis, Mo

Soups

Cream, meat, or vegetable soups prepared at home without eggs or egg products (such as noodles).

Sugars

Brown, granulated, powdered, and maple. Homemade jellies, jams, and preserves.

Vegetables

All kinds, canned, cooked or raw, prepared with cream, milk, or butter. Do not combine with eggs

Forbidden Foods

Baking Powder . . . Except Royal

Beverages

Coffee, if egg white has been used to clarify it Root beer which may have had egg added to make it foam Malted drinks or any prepared drink made with eggs or egg powders

Breads

Commercial breads that have egg as an ingredient or have been brushed with egg white to glaze the top

Breaded Foods

If the breading used is an egg mixture.

Broth or Consommé

All broth and consommé unless certified as free of eggs Also soups that have been cleared with egg

Candies

Commercial candies brushed with egg white to give them luster—bonbons, almond cakes, fondants, pastes, marshmallows

Desserts

Bavarian cream, blanc mange, cakes, cookies, custards, doughnuts, or frostings made with eggs

Dishes Prepared with Eggs

Baked, coddled, creamed, deviled, escalloped, fried, poached, scrambled, shirred, hard- or soft-cooked eggs, egg drinks, egg sauces, egg whips or omelets Do not use dried or frozen eggs in any foods

Ice Cream

Ice cream, ices, and sherbets, unless made at home without eggs from an egg-free powder

Meats

Sausage, wiener schnitzel, meat loaf, croquettes, or ready-prepared meats packed in casing that may contain egg white

Miscellaneous

Griddle cakes, dumplings, pretzels, noodles, marshmallows, soufflé, French toast, fritters, prepared mixes for biscuits, cakes, cookies, doughnuts, muffins, or pie crust

Pastries

Macaroons, meringues, or pies (such as custard, lemon, coconut, and pumpkin) Puddings, unless homemade without eggs Spanish cream, timbales, waffles

Salad Dressings

All salad dressings unless homemade without eggs

Sauces

Hollandaise sauce, Tartar sauce, mayonnaise.

Soups

Mock Turtle, consommé, bouillon, noodle, or any soup made with egg or from ingredients containing egg

TABLE 9

THE WHEAT, EGG, AND MILK FREE DIET *

If You Are Sensitive to Wheat, Eggs, and Milk, You May Eat the Following Foods:

These foods must be prepared without the use of wheat products, eggs, and dairy products

Beverages

Cocoa made with water, coffee or tea without cream or milk, fresh or bottled fruit juices mineral or carbonated waters

Breads

Without wheat, eggs, or milk, cornbread or cornpone, rice, Ry-Krisp, or whole rye (Use recipes found in Table 13, or those prescribed by your physician)

Candies

Made without dairy products, such as fondant, molasses taffy, French paste

Cereals

Barley, barley flour; cornflakes, cornmeal, cornstarch, potato flour, rice, rice flakes, rolled oats, rye; tapioca, crumbled Ry-Krisp wafers

* Courtesy Ralston Purina Co, St Louis Mo

Condiments

Anchovy; anise, caraway, chili sauce; homemade catsup or tomato relish made without wheat products, cinnamon; cloves; garlic; ginger; horseradish, mint; mustard, nutmeg; paprika, pepper; pimiento; poppy seed, sage; salt; vanilla.

Desserts

Fruit gelatins, fruit ices; fruit pudding †; Indian pudding, oatmeal, rice or rye cookies, Ry-Krisp pastry †; candied apple betty †, tapioca.

Fats

Meat (bacon or lard), poultry or vegetable fats; olive or other salad oils.

Fruits

All kinds, raw, canned, or plain; cooked with sugars, honey, or syrups, without milk or cream.

Meats

All meats may be eaten if they *are not* prepared with wheat, eggs, or milk products Do not use ready-prepared meats, such as cervelat, hamburger, meat loaf, and sausages, as they frequently contain wheat products as fillers

Note: Ry-Krisp wafers, rolled *into* crumbs. are excellent for breading meats or fish.

Nuts

All kinds.

Olives

Green, ripe, or stuffed.

Pickles

All kinds.

Poultry and Game

All kinds prepared without wheat, eggs, or milk

Seafoods

All kinds prepared without wheat, eggs, or milk

Soups

Home made meat and vegetable soups

Sugars

Brown, granulated, powdered, confectioner's, and maple.
Homemade jellies, jams, and preserves
Honey
Corn or maple sugars

Vegetables

All kinds canned, cooked, or raw, prepared without wheat, eggs, or milk.

† Recipe will be found in Table 13

If You Are Sensitive to Wheat, Eggs, and Milk, DO NOT EAT:

Beverages

Cereal beverages or coffee substitutes made from wheat. (Information as to ingredients may be found on can or package)
Chocolate or cocoa—as a beverage (unless made with water)
Malted milk drinks

Breads

Hot breads such as muffins, popovers, baking-powder biscuits, made with wheat products, griddle cakes, waffles, doughnuts
Wheat breads—This will include the following
Corn bread (unless made at home without the use of wheat flour)
Crackers of all kinds (this does not include Ry Krisp)
Gluten bread.
Graham bread
Pretzels
Rye bread (unless home-made with only rye flour)
White bread.
Whole-wheat bread.
Zwieback

Candies

Candies (unless you are *certain* they do not contain dairy products)

Cereals

Cereals—all dry or cooked cereals made from or containing whole wheat, farina, or bran

Dairy Products

Butter
Buttermilk.
Cheese
Condensed, evaporated, or dried milk.
Cream.
Curd
Milk, whole or skimmed.
Powdered or malted milk.
Whey.
Ice cream and sherbets

Desserts and Pastries

Cakes
Cookies, including macaroons.
Custards
Dumplings.
Frostings, unless made without milk or eggs
Ice cream
Milk or cream sherbets.
Spanish cream
Bavarian cream.
Marshmallows.
Meringues
Puddings (unless made without milk, wheat, or eggs)
Pastries of all kinds, including pies

Egg Dishes

Baked.
Coddled.
Creamed.
Deviled
Egg drinks.
Egg sauces.
Egg whips.
Escalloped.
Fried
Hard or soft cooked
Omelets
Poached
Scrambled
Shirred.

Note. Do not use dried or frozen eggs in any foods.

Salad Dressings

Mayonnaise
Boiled salad dressing

Sauces

Gravies made with wheat products
Cream sauces
Hollandaise sauce.
Hard sauces.

Soups

Bisques.
Chowders, unless made without milk
Milk or cream soups.

Dishes Prepared with Milk or Eggs

Escalloped dishes.
Creamed foods.
Food prepared au gratin.
Rarebits.
Soufflés.
Timbales.

Wheat Products

Bread crumbs
Buckwheat.
Cracker crumbs.
Cracker meal.
Graham flour.
Macaroni
Noodles (including alphabet noodles).
Spaghetti
Vermicelli.
Wheat flour in any form—whole wheat, graham, or white, or any mixture of grain flours that may have wheat content.

Miscellaneous

Baking powder, except Royal, which does not contain egg
Breaded foods, in which the adherent used has been an egg mixture
Fritters
Malt products
Yeast cakes
Oleomargarine, if churned in milk

TABLE 10

WHEAT-FREE RECIPES *

Ry-Krisp † Crumb Crust

¾ cup Ry-Krisp flour	Few grains salt
1 tablespoon vegetable shortening	¼ cup water

Put Ry-Krisp wafers through food chopper, then roll to a flour with rolling pin Work shortening into flour with pastry blender or fingers Add salt and water and blend well with a spoon Put in tart shell and press down evenly all around Add fruit filling and bake in a moderate oven (350° F.) until tender Sufficient for three tarts about 3 inches in diameter

Note Fill with sliced apples, to which a few raisins may be added, and sugar and cinnamon Dot with vegetable shortening Or fill with sweetened sliced peaches or apricots

Gravy

3 Ry Krisp wafers	1 cup meat stock, or water
1 tablespoon shortening	¼ teaspoon salt

Few grains pepper

Put Ry-Krisp wafers through food chopper, then roll [illegible]

Note An equal quantity of Ry-Krisp crumbs may be substituted for ordinary flour in thickening soups, sauces, etc

White Sauce

(for creaming vegetables, fish, meat, or eggs)

1 tablespoon butter	¾ teaspoons salt
1½ teaspoons cornstarch	½ cup milk

Melt butter in saucepan Blend in cornstarch and salt. Stir in milk slowly Bring to a boil, stirring constantly Boil slowly for 5

* Courtesy [illegible]

minutes, stirring frequently. Makes sufficient for creaming a cup of cooked or canned vegetables, fish, diced meat, or sliced hard-cooked eggs.

Note: Potato or rice flour may be substituted for the cornstarch

For Spiced White Sauce, cook ½ teaspoon finely cut onion slowly in the butter before blending in the cornstarch and salt. Stir in the milk Then add 2 whole cloves and a few grains of cayenne pepper and boil as directed above

Virginia Spoon Bread

2 cups milk	½ cup cornmeal
¾ teaspoon salt	3 eggs, separated

Heat milk to boiling point. Add salt Add cornmeal so slowly that mixture does not stop boiling. Boil, stirring constantly, until mixture thickens, about 2 minutes. Beat egg whites until stiff, then beat egg yolks until light and fluffy Stir cornmeal mixture slowly into the beaten egg yolks Fold in stiffly beaten egg whites Pour into a greased 8-inch baking dish. Bake in a moderately slow oven (350° F) 1 hour, or until brown and firm to the touch Serve warm from the dish. Serves 6

Sagebrush Turkeys

1 cup Ry-Krisp crumbs (about 12 wafers)	1 teaspoon vegetable shortening
¼ cup hot meat stock, or water	½ green pepper, chopped
½ small onion, minced	Sage and pepper to taste
	3 slices lean bacon

To the crumbs add hot stock, onion, shortening, green pepper, and seasonings Mold dressing into three small cylinders Wrap with bacon, using 1 slice for each, and secure with toothpicks Place in baking dish and bake in a hot oven (400° F) until bacon is crisp and brown. *Serves three.*

Note. These may be served with tomato sauce thickened with cornstarch or Ry-Krisp crumbs rolled to a flour

Cinnamon Toast

4 tablespoons sugar	2 teaspoons cinnamon
4 Ry-Krisp wafers	

Mix sugar and cinnamon together Brush Ry-Krisp wafers with vegetable oil or shortening and bake in a moderate oven (350° F) until light brown. Sprinkle on sugar mixture while warm

Coffee Spice Cake

2 cups potato flour	½ cup soft butter or other shortening
4 teaspoons baking powder	1 cup sugar
¾ teaspoon salt	2 well beaten eggs
1 teaspoon cinnamon	½ cup strong black coffee

[illegible]

alternately with coffee, beginning and ending with flour mixture Beat until smooth after each addition Spread batter in greased pan 8 x 8 x 2 inches deep. Bake in a moderate oven (375° F.) 45 minutes, or until cake shrinks from sides of pan.

Sour Cream Cookies

⅔ cup rye flour	⅔ cup sugar
½ cup rice flour	1 well beaten egg
½ cup cornstarch	⅓ cup thick sour cream
1 teaspoon baking powder	1 tablespoon sugar
¼ teaspoon salt	¼ teaspoon cinnamon

⅓ cup butter or other shortening

Sift flours and cornstarch separately before measuring Resift with baking powder and salt Cream butter and sugar together until light and fluffy Add beaten egg Then add flour mixture alternately with cream, beginning and ending with flour mixture. Beat until smooth after each addition Drop by teaspoons on greased baking sheet Flatten slightly with bottom of glass which has been dipped in sugar. Mix the tablespoon of sugar with cinnamon and sprinkle a small amount on top of each cooky Bake in moderate oven (375° F) 15 minutes, or until brown Makes about 3 dozen

Cocoanut Macaroons

2 egg whites	2 tablespoons cornstarch
¾ cup sugar	¼ teaspoon cream of tartar

2 cups shredded cocoanut

Beat egg whites until stiff Add gradually a mixture of sugar, cornstarch, and cream of tartar Cook over boiling water 10 min-

utes, stirring frequently. Remove from heat and fold in the cocoanut gradually. Drop from a teaspoon on greased baking sheet Bake in moderately slow oven (350° F.) 10 minutes, or until lightly browned Makes about 1½ dozen

Meat or Poultry Stuffing

2 dozen Ry-Krisp wafers	1 onion, chopped
¾ cup hot meat stock, or water	¼ cup chopped celery
¼ cup vegetable shortening	2 tablespoons chopped parsley
1 green pepper, chopped	Sage and pepper to taste

Put Ry-Krisp wafers through food chopper, then soak in hot stock Add remaining ingredients and mix well Sufficient for stuffing a 3-pound bird.

Fruit Pudding

1 cup Ry-Krisp crumbs (about 12 wafers)	¼ cup seedless raisins
¾ cup pineapple juice	¼ cup chopped nuts
2 tablespoons brown sugar	¼ cup each cloves, cinnamon, and nutmeg

Soak crumbs in pineapple juice until soft Add remaining ingredients and put into a baking dish greased with vegetable shortening Cover and set in pan containing sufficient water to come within an inch of the top of baking dish Steam 1½ hours and serve warm. Serves three Serve with Fruit Sauce

Note: Mixture may be put in the top part of a double boiler, covered tightly, and cooked slowly over boiling water.

TABLE 11

MILK-FREE RECIPES *

Sponge Cake

1 cup cake flour	4 eggs, separated
¼ teaspoon salt	1 cup sugar

4 teaspoons lemon juice

Sift flour before measuring Resift with salt Beat egg yolks until thick and lemon colored Add sugar gradually, beating constantly

* Courtesy, Ralston Purina Co, St Louis, Mo

Add lemon juice and mix thoroughly. Fold in flour, alternately with stiffly beaten egg whites. Do not beat, but bake at once in a floured, ungreased loaf pan, about 8 x 4 x 3 inches deep, in a slow oven (325° F) 40 to 60 minutes

Gingerbread

½ cup vegetable shortening	1½ teaspoons baking soda
½ cup brown sugar	½ teaspoon salt
2 eggs, well-beaten	1½ teaspoons ginger
1 cup molasses	1 teaspoon cinnamon
2½ cups whole-wheat flour	1 cup boiling water

[illegible]

greased pan about 9 inches square and bake in moderate oven (350° F) 30 to 40 minutes

Plain Omelet

2 eggs, separated	¼ teaspoon salt
2 tablespoons hot water	Few grains pepper

Beat egg yolks until thick and lemon colored Add water and seasonings Beat egg whites until stiff and dry Fold whites into egg-yolk mixture Pour into hot greased omelet or frying pan and spread evenly Cook over low heat until omelet is a golden brown on the under side Place in a moderate oven (350° F) until top is dry and firm Loosen from pan with spatula and turn out on platter Serve at once Serves two

Stuffed Tomatoes

3 tomatoes	½ tablespoon chopped onion
¾ cup Ry Krisp † crumbs	⅛ teaspoon pepper
1 tablespoon chopped green pepper	1 tablespoon vegetable shortening

Cut off stem end of each tomato and carefully remove centers Mix the centers of the tomatoes with crumbs, seasonings, and

† Ry Krisp is indicated as a safe bread for allerg[illegible] is made [illegible]

melted shortening. Sprinkle each tomato with salt and pepper and fill with t[illegible] ening on the t[illegible] an inch of hot [illegible] tender. Serves three

Meat or Poultry Stuffing

- 2 dozen Ry-Krisp wafers
- ¾ cup hot meat stock, or water
- ¼ cup vegetable shortening
- 1 green pepper, chopped
- 1 onion, chopped
- ¼ cup chopped celery
- 2 tablespoons chopped parsley
- Sage and pepper to taste

Put Ry-Krisp wafers through food chopper, then soak in hot stock. Add remaining ingredients and mix well. Sufficient for stuffing a 3-pound bird.

Sweet Potato Casserole

- ¼ cup brown sugar, lightly packed
- 3 tablespoons orange juice
- 2 tablespoons butter
- 3 cups mashed sweet potatoes, cooked or canned
- ¾ teaspoon salt
- 3 ripe bananas (medium-sized)

Heat sugar, orange juice, and butter together until sugar and butter are melted. Add to mashed sweet potatoes and salt. Mix well. Arrange sweet potatoes and bananas, sliced crosswise, in alternate layers in greased 8-inch baking dish, having potatoes on top. Bake in moderate oven (375° F.) about 25 minutes. Serves six.

Note: Cook 3 large sweet potatoes to make 3 cups when mashed.

For Pineapple Sweet Potatoes, substitute pineapple juice for orange juice and 1½ cups diced pineapple for the bananas.

Prune Whip

- ¾ cup dried prunes
- 1¾ cups water
- 1 tablespoon plain, unflavored gelatin
- 2 tablespoon lemon juice
- 1 teaspoon grated lemon rind
- ½ cup sugar
- ⅛ teaspoon salt
- 2 egg whites, stiffly beaten

Cook prunes in 1½ cups water about 45 minutes, or until tender. Meanwhile, soak gelatin in remaining ¼ cup water. Drain prunes,

and save juice There should be ¾ cup juice. If not, add water. Pit prunes, then rub through coarse wire strainer. Mix prune juice and pulp, lemon juice and rind, sugar and salt. Cook 2 minutes, stirring constantly Stir in soaked gelatin. Chill until mixture begins to thicken, then fold in stiffly beaten egg whites Pile in sherbet glasses and keep chilled until serving time. Serves six

For Prune Chiffon Pie, pile Prune Whip in Ry-Krisp Crumb Crust Chill until firm

Fruit Pudding

1 cup Ry-Krisp crumbs (*about 12 wafers*)
¾ cup pineapple juice
2 tablespoons brown sugar
¼ cup seedless raisins
¼ cup chopped nuts
¼ teaspoon each cloves, cinnamon, and nutmeg

Note Mixture may be put in the top part of a double boiler, covered tightly, and cooked slowly over boiling water

Candied Apple Betty

2 large, tart apples
¼ cup brown sugar
½ cup Ry-Krisp crumbs
¼ cup vegetable shortening

Pare apples and slice thin Cream shortening and sugar thoroughly and add Ry-Krisp crumbs Arrange alternate layers of sliced apples and Ry-Krisp mixture in greased baking dish, having apples on the bottom and sugar mixture on top Bake in a moderate oven (325° F) about ½ hour Serves three

Note Canned or fresh sliced peaches may be substituted for the apples

TABLE 12

EGG-FREE RECIPES *

Eggless Mayonnaise

¼ cup evaporated milk
1 teaspoon salt
½ teaspoon paprika
1 teaspoon sugar
1⅛ teaspoons dry mustard
Few grains cayenne
1 cup salad oil
1 tablespoon lemon juice
1 tablespoon vinegar

Put evaporated milk in mixing bowl, then add salt, paprika, sugar, mustard, and cayenne Add oil drop by drop, until mixture thickens a little Mix lemon juice and vinegar together. Add alternately with the oil, 1 teaspoonful at a time, until all are used, beating thoroughly after each addition. Ingredients should be cold. While mixing, set the bowl in a pan of cold water. Keep in refrigerator until ready to serve. Makes about 2 cups

Ry-Krisp † Crumb Crust

12 Ry-Krisp wafers
¼ cup sugar
⅓ cup melted butter

Roll wafers into fine crumbs to make 1 cup crumbs Fold in sugar Then add melted butter and mix thoroughly With back of spoon press on bottom and sides of deep, buttered, 9-inch pie pan Chill thoroughly Fill with fruit or gelatin filling.

Apple Tapioca

3 medium-sized apples (¾ lb)
3 cups boiling water
2 tablespoons lemon juice
3 tablespoons butter
1¼ cups light brown sugar, lightly packed
½ cup quick-cooking tapioca
1 teaspoon salt
¼ teaspoon nutmeg
¼ teaspoon cinnamon

* Courtesy, Ralston Purina Co, St Louis Mo
† Ry-Krisp is indicated as a safe bread for allergy diets because it is made simply of flaked rye, water, and salt Rolled, ground, or crumbled and used as flour, Ry-Krisp is also a safe ingredient in preparing many wheat-, egg-, and milk-free dishes Ry-Krisp is available at most food stores throughout the United States.

Pare, core, and slice apples Put in greased 8-inch baking dish Add boiling water, lemon juice and 2 tablespoons of the butter Cover and bake in a moderately slow oven (350° F.) 25 minutes, or until apples are almost tender Remove cover and stir in a mixture of 1 cup of the sugar, the tapioca, salt, and spices Mix [illegible]

clear Serve warm or cold. Serves six

Orange Custard

2 tablespoons cornstarch	¾ cup evaporated milk
¼ cup sugar	¾ cup orange juice
⅛ teaspoon salt	1 teaspoon grated orange rind

Mix thoroughly cornstarch, sugar, and salt Add ¼ cup milk and blend until smooth Heat remaining milk in double boiler Add cornstarch mixture and cook until it begins to thicken Add orange juice and grated rind and cook until thick, stirring constantly to avoid lumping Cover and cook 20 minutes Turn into cold, wet molds and chill Serves three.

Molasses Pudding

2 slices whole-wheat bread, ¾ inch	1 cup milk
1 tablespoon butter	2 tablespoons molasses

Spread bread with butter and cut in cubes Arrange in greased baking dish Mix milk and molasses together, and pour over bread Bake in a slow oven (325° F) 40 minutes, stirring twice during first half hour Serves two.

Butterscotch Icebox Cookies

3 dozen Ry-Krisp wafers	1 teaspoon soda
½ cup rye flour	½ teaspoon salt
½ cup rice flour	½ teaspoon vanilla
1 cup light brown sugar, lightly packed	¾ cup melted butter
	⅓ cup boiling water

Roll Ry-Krisp wafers into crumbs Sift rye and rice flour before measuring Resift with sugar, soda, and salt. Mix thoroughly with Ry Krisp crumbs Mix melted butter, vanilla, and boiling water

together. Add to dry ingredients and mix well. Shape into a roll about 12 inches long and 2 inches in diameter. Wrap in waxed paper. Chill until firm, about 4 hours or overnight. When firm, cut into thin slices. Put on greased baking sheets about an inch apart. Bake in a moderate oven (375° F.) 15 minutes, or until brown Makes about 5 dozen.

For Spice Icebox Cookies, substitute granulated sugar for the brown and sift ½ teaspoon *each of nutmeg and cinnamon* with the flour mixture Omit vanilla. Mix and bake as directed above.

Eggless Spice Cake

- 1 cup light brown sugar, lightly packed
- 1¼ cups water
- 1 cup seedless raisins
- ⅓ cup shortening
- ⅔ cup rye flour
- ⅔ cup rice flour
- ⅔ cup cornmeal
- 2 teaspoons Royal baking powder ‡
- ½ teaspoon salt
- 1 teaspoon nutmeg
- 1 teaspoon cinnamon

Mix together in a saucepan the sugar, water, raisins, and shortening Bring to a boil while stirring Then boil 3 minutes Cool Meanwhile, sift rye and rice flour separately before measuring Resift with cornmeal, baking powder, salt, and spices Add to cooled sugar mixture Mix quickly but thoroughly Put in greased baking pan 8 x 8 x 2 inches deep Bake in moderately slow oven (350° F) 45 minutes, or until cake shrinks from sides of pan

Fruit Sauce

(for Fruit Pudding, boiled rice, or other allowed cereals or desserts)

- 1 cup fruit juice, such as pineapple, cherry, peach, apricot, prune, or grape
- 2 tablespoons brown sugar
- 1 teaspoon cornstarch

Heat the juice with the sugar. Add cornstarch, which has been mixed to a smooth paste with 2 tablespoons of the hot fruit juice, stirring constantly. Cook slowly 10 minutes, stirring occasionally Serve warm on Fruit Pudding

‡ Royal baking powder is suggested because it is the most widely distributed baking powder containing no egg whites.

Fruit Pudding

1 cup Ry-Krisp crumbs (about 12 wafers)	½ cup seedless raisins
¾ cup pineapple juice	½ cup chopped nuts
2 tablespoons brown sugar	¼ teaspoon each cloves, cinnamon, and nutmeg

Soak crumbs in pineapple juice until soft. Add remaining ingredients and put into a baking dish greased with vegetable shortening. Cover and set in pan containing sufficient water to come within an inch of the top of baking dish. Steam 1½ hours and serve warm. Serves three. Serve with Fruit Sauce.

Note. Mixture may be put in the top part of a double boiler, covered tightly, and cooked slowly over boiling water.

Candied Apple Betty

2 large, tart apples	½ cup Ry-Krisp crumbs
¾ cup brown sugar	¼ cup vegetable shortening

Pare apples and slice thin. Cream shortening and sugar thoroughly and add Ry-Krisp crumbs. Arrange alternate layers of sliced apples and Ry-Krisp mixture in greased baking dish, having apples on the bottom and sugar mixture on top. Bake in a moderate oven (325° F.) about ½ hour. Serves three.

Note. Canned or fresh sliced peaches may be substituted for the apples.

TABLE 13

RECIPES WITHOUT WHEAT, EGGS, OR MILK *

Cinnamon Toast

4 tablespoons sugar	2 teaspoons cinnamon
4 Ry-Krisp wafers	

Mix sugar and cinnamon together. Brush Ry-Krisp † wafers with vegetable oil or shortening and bake in a moderate oven (350° F.) until light brown. Sprinkle on sugar mixture while warm.

* Courtesy, Ralston Purina Co., St. Louis, Mo.

† Ry-Krisp, the whole-rye wafer which features rather prominently in the above recipes, is made of whole rye, water, and salt, and may

Rye and Rice Muffins ‡

- ⅓ cup rice flour
- ⅔ cup rye flour
- 6 teaspoons Royal baking powder §
- 4 teaspoons sugar
- ¼ teaspoon salt
- ⅔ cup water
- ½ tablespoon vegetable shortening, melted

Sift dry ingredients together. Add water and melted shortening and beat thoroughly. Pour into muffin tins greased with vegetable shortening and bake in a hot oven (400° F.) 25 minutes. Makes six muffins, 2 inches in diameter.

Rye Rice Bread ‡

- 1⅓ cups rye flour
- ⅔ cup rice flour
- ½ teaspoon salt
- 6 teaspoons sugar
- 10 teaspoons Royal baking powder
- 1⅓ cups water
- 2 teaspoons olive oil

Sift dry ingredients together. Add water and oil, beating thoroughly. Pour into loaf pan greased with olive oil and bake in a moderate oven (350° F.) 40 minutes. Makes one loaf.

Rice and Cornmeal Muffins ‡

- 1⅓ cups rice flour
- ⅔ cup cornmeal
- ½ cup sugar
- ½ teaspoon salt
- 10 teaspoons Royal baking powder
- 1 cup water
- ¼ cup olive oil

Sift dry ingredients together. Add water and oil and beat 3 minutes. Pour into muffin tins, greased with olive oil, and bake immediately in a moderate oven (350° F.) 30 minutes. Makes one dozen muffins, 2 inches in diameter.

Cornpone

- ¼ cup cornmeal
- ⅓ teaspoon salt
- ½ cup boiling water

be safely used in wheat-, egg-, and milk-free diets. It comes in a red-and-white checkerboard package and can be purchased at your grocery store.

‡ Recipes for rye and rice muffins, rye rice bread, and rice and corn- [illegible] Food Allergy, Philadelphia Lea &

[illegible] sted because it is the most widely [illegible] ing no egg whites

Sift cornmeal and salt together Add boiling water to make a firm mixture Shape into thin cakes, place in pan well greased with bacon fat, and bake in a hot oven (400° F.) 15 to 20 minutes Makes four small cakes

Stuffed Tomatoes

3 tomatoes	½ tablespoon chopped onion
¾ cup Ry-Krisp crumbs	¼ teaspoon pepper
1 tablespoon chopped green pepper	1 tablespoon vegetable shortening

Cut off stem end of each tomato and carefully remove centers. Mix the centers of the tomatoes with crumbs, seasonings, and melted shortening Sprinkle each tomato with salt and pepper and fill with the mixture Place a small piece of vegetable shortening on the top of each, arrange in baking dish containing half an inch of hot water, and bake in a moderate oven (350° F.) until tender Serves three

Note For *Stuffed Onions*, remove slice from the top of each and parboil until tender Drain, then remove centers and proceed as above

Gravy

2 tablespoons Ry-Krisp flour	1 cup meat stock or water
1 tablespoon vegetable shortening	Salt and pepper

Put Ry-Krisp wafers through food chopper, then roll fine with rolling pin About 3 wafers will be needed to make 2 tablespoons of flour Blend shortening in which meat was cooked, or other shortening, with the flour Add meat stock slowly and stir until thick Season with salt and pepper Makes 1 cup of gravy

Note An equal quantity of Ry-Krisp flour may be substituted for ordinary flour in thickening soups, sauces, etc.

Meat or Poultry Stuffing

2 dozen Ry-Krisp wafers	1 onion, chopped
¾ cup hot meat stock or water	¼ cup chopped celery
¼ cup vegetable shortening	2 tablespoons chopped parsley
1 green pepper, chopped	Sage and pepper to taste

Put Ry-Krisp wafers through food chopper, then soak in hot

Rye and Rice Muffins ‡

⅓ cup rice flour
⅔ cup rye flour
6 teaspoons Royal baking powder §
4 teaspoons sugar
¼ teaspoon salt
⅔ cup water
½ tablespoon vegetable shortening, melted

Sift dry ingredients together. Add water and melted shortening and beat thoroughly. Pour into muffin tins greased with vegetable shortening and bake in a hot oven (400° F) 25 minutes Makes six muffins, 2 inches in diameter

Rye Rice Bread ‡

1⅓ cups rye flour
⅔ cup rice flour
½ teaspoon salt
6 teaspoons sugar
10 teaspoons Royal baking powder
1⅓ cups water
2 teaspoons olive oil

Sift dry ingredients together Add water and oil, beating thoroughly. Pour into loaf pan greased with olive oil and bake in a moderate oven (350° F) 40 minutes Makes one loaf

Rice and Cornmeal Muffins ‡

1⅓ cups rice flour
⅔ cup cornmeal
½ cup sugar
½ teaspoon salt
10 teaspoons Royal baking powder
1 cup water
¼ cup olive oil

Sift dry ingredients together Add water and oil and beat 3 minutes Pour into muffin tins, greased with olive oil, and bake immediately in a moderate oven (350° F) 30 minutes Makes one dozen muffins, 2 inches in diameter

Cornpone

¼ cup cornmeal
⅓ teaspoon salt
½ cup boiling water

be safely used in wheat-, egg-, and milk-free diets It comes in a red-and white checkerboard package and can be purchased at your grocery store

‡ Recipes for rye and rice muffins, rye rice bread, and rice and corn- ... Food Allergy, Philadelphia Lea &

... ted because it is the most widely
... ng no egg whites

added, and sugar and cinnamon. Dot with vegetable shortening Or fill with sweetened sliced peaches or apricots.

Fruit Pudding

1 cup Ry-Krisp crumbs (about 10 wafers)	¼ cup seedless raisins
¾ cup pineapple juice	¼ cup chopped nuts
2 tablespoons brown sugar	¼ teaspoon each cloves, cinnamon and nutmeg

Soak crumbs in pineapple juice until soft. Add remaining ingredients and put into a baking dish greased with vegetable shortening Cover and set in pan containing sufficient water to come within an inch of the top of baking dish. Steam 1½ hours and serve warm. Serves three Serve with Fruit Sauce.

Note. Mixture may be put in the top part of a double boiler, covered tightly, and cooked slowly over boiling water

Fruit Sauce

(for Plum Pudding, boiled rice, or other allowed cereals or desserts)

1 cup fruit juice, such as pineapple, cherry, peach, apricot, prune or grape	2 tablespoons brown sugar
	1 teaspoon cornstarch

Heat the juice with the sugar. Add cornstarch, which has been mixed to a smooth paste with 2 tablespoons of the fruit juice, stirring constantly Cook slowly 10 minutes, stirring occasionally. Serve warm on Fruit Pudding

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General Avoidance Instructions. General directions are given to each patient emphasizing certain avoidance advice as follows

Use no insect powder in any part of the house without specific permission This includes fly sprays, roach and ant powders, dog flea powders, and certain other types of mothproofing preparations. As far as it is possible, none of the substances to which the patient is sensitive should be found in the home.

stock. Add remaining ingredients and mix well. Sufficient for stuffing a 3-pound bird.

Sagebrush Turkeys

- 1 cup Ry-Krisp crumbs (about 10 wafers)
- ¼ cup hot meat stock or water
- ½ small onion, minced
- 1 teaspoon vegetable shortening
- ½ green pepper, chopped
- Sage and pepper to taste
- 3 slices lean bacon

To the crumbs add hot stock, onion, shortening, green pepper, and seasonings Mold dressing into three small cylinders Wrap with bacon, using 1 slice for each, and secure with toothpicks. Place in baking dish and bake in a hot oven (100° F.) until bacon is crisp and brown Serves three

Note: These may be served with tomato sauce thickened with cornstarch or Ry-Krisp crumbs rolled to a flour

Candied Apple Betty

- 2 large, tart apples
- ¾ cup brown sugar
- ½ cup Ry-Krisp crumbs
- ¼ cup vegetable shortening

Pare apples and slice thin. Cream shortening and sugar thoroughly and add Ry-Krisp crumbs Arrange alternate layers of sliced apples and Ry-Krisp mixture in greased baking dish, having apples on the bottom and sugar mixture on top Bake in a moderate oven (325° F) about one-half hour Serves three

Note: Canned or fresh sliced peaches may be substituted for the apples.

Ry-Krisp Pie Crust

- ¾ cup Ry-Krisp flour
- 1 tablespoon vegetable shortening
- Few grains salt
- ¼ cup water

Put Ry-Krisp wafers through food chopper, then roll to a flour with rolling pin. Work shortening into flour with pastry blender or fingers. Add salt and water and blend well with a spoon Put in tart shell and press down evenly all around Add fruit filling and bake in a moderate oven (350° F) until tender. Sufficient for three tarts about 3 inches in diameter.

Note. Fill with sliced apples, to which a few raisins may be

by feeding the patient a very small quantity of the offending food in an extremely high dilution, such as one teaspoonful of 1-1,000 milk dilution three times a day, gradually increasing the dose. The method of "desensitization" is employed to advantage in allergy to inhalants. This method of therapy, referred to as specific "desensitization," or more correctly "hyposensitization," consists in the subcutaneous administration of gradually increasing doses of the offending allergen at weekly intervals, beginning with a dilution sufficiently high to safeguard the patient from constitutional reaction. This procedure is used particularly in the treatment of patients sensitive to dust and other inhalants. Individuals sensitive to house dust are instructed to bring to the office about a quart of dust collected with the vacuum sweeper from carpets, mattresses, and drapes. An autogenous extract is prepared from this material. House-dust extract is administered subcutaneously either in a 1-10 dilution or in the concentrated form, depending on the degree of sensitivity shown by the patient. The first dose is 0.1 cc., increasing every week by 0.1 cc. until 1.0 cc. dose is reached. This dose is given every week for four treatments, then every two weeks, every three weeks, and every four weeks for four treatments. If the arm becomes sore or swollen at the point of *injection*, or if the patient develops a constitutional reaction, the subsequent dose is not increased but reduced, depending on the extent of the reaction.

Nonspecific "Desensitization." On a purely *empiric* basis, nonspecific "desensitization" *may also* be carried out with such agents as respiratory (nasal and sputum) VACCINES, both autogenous and stock, with PEPTONE, TUBERCULIN, MILK, etc. Respiratory vaccines are administered subcutaneously in a dilution of 1-10 *or in* concentrated form. The first dose is 0.1 cc., increasing every week by 0.1 cc. until a 1.0 cc. dose is reached. This dose is given every week for

No fresh or artificial (dust catcher) flowers should be kept in the house. Use only washable toys (remove all stuffed or hair fabric toys). Avoid contact with irritating odors from leaking stoves and electric refrigerators, kerosene lamps, fresh paint, tobacco smoke, camphor, tar, etc. Do not keep any animal pets in your home unless specifically permitted.

Do not indulge in any physical exertion which makes you short of breath or causes you to become overheated.

Do not hurry, walk slowly and stop occasionally.

Protect yourself against exposure to changes in weather so that you do not catch colds.

Do not use mustard plasters or flaxseed poultices.

Take drugs only upon prescription, for harmless medicine may be injurious to you.

Avoid perfumes, face powders, sachet, and scented talcum powders, shaving and shampoo soaps, toothpaste, toilet water and scented soaps Many of these contain orris root and rice powder. Use only those specifically recommended.

Avoid all dusty and musty places (Basements, storerooms, attics, etc.)

Avoid all contacts and foods listed for you.

Avoid swimming *unless specifically* permitted.

Do not overload your stomach with heavy meals.

Avoid carbonated waters, such as seltzer, cola, pop, ginger ale, etc.

Consult your physician if troubled by constipation.

Use no condiments, spices, peppers, sauces, mustards, pickles, or any other highly seasoned foods

"DESENSITIZATION"

Specific "Desensitization." The treatment of food allergy is accomplished by proper avoidance "*Desensitization*" is rarely resorted to except, perhaps, in infants sensitive to milk or eggs. In these instances tolerance may be developed

Benzedrine. This may be employed to advantage for nasal inhalation, but because of its stimulating effect on the nervous system it should be used with caution.

Atropine. This alkaloid, contained in belladonna and stramonium, acts primarily through inhibition of the parasympathetic (vagus) nervous system. It paralyzes the various nerve endings in the bronchi and bronchial glands, thus relieving bronchospasm and reducing the secretion of the hyperactive bronchial mucous glands in asthma. It may be administered by mouth, in the form of extract of belladonna, in doses of gr. 1/6 to 1/4 in combination with ephedrine and phenobarbital. This combination is particularly effective in hay fever and allergic rhinitis. Stramonium-containing powders which are ignited and then inhaled are sometimes of value in asthma.

Narcotics. CODEIN and MORPHINE are indicated only in very small doses and in special cases, to relieve the extreme anxiety and irritability which are not alleviated by the usual sedatives. Certainly the indiscriminate and repeated use of opiates in asthma is contraindicated, not only because their use in chronic conditions may easily become habit forming, but also because they have been found to aggravate rather than to relieve the paroxysm of asthma. The patient in status asthmaticus is fighting for breath. He has difficulty in breathing because his bronchial tree is in a large measure occluded through the accumulation of thick, tenacious mucous plugs. The purpose of treatment in these severe cases is to thin out the mucus, liquefy it, and lead to its expulsion through the process of coughing. Opiates abolish the cough reflex and for this reason defeat the purpose of treatment. Furthermore, they slow the respiratory rate, an effect which, in a severe case of asthma, may prove very serious. However objectionable the administration of morphine may be in bronchial asthma, its use in cardiac asthma or paroxysmal nocturnal cardiac dyspnea

hour if the first dose does not give complete relief. Massaging the skin at the point of injection will give occasional relief because of increased reabsorption.

The patient must be instructed in the proper use of epinephrine 1-100 by nebulizer. Three to five drops of this solution of the drug are introduced into the glass nebulizer with a medicine dropper. The patient places the nozzle of the nebulizer into the mouth and pumps the bulb three or four times while inhaling deeply. The purpose is to inhale the maximum amount of the vapor produced by the nebulizer. Some patients complain of a bitter dry taste following the use of this preparation. For this reason it is suggested that the patient be instructed to rinse his mouth with water following each inhalation The nebulizer may be used again within 15 to 30 minutes if relief is not obtained. It should be cleaned with warm water or vinegar.

Ephedrine. Like epinephrine, ephedrine stimulates the sympathetic nervous system, producing vasoconstriction and bronchial dilatation. It has the advantage of being more stable and suitable for oral administration than epinephrine. In some instances it has powerful side-effects, producing severe nervous manifestations and insomnia. In these cases one may employ some of the synthetic ephedrine preparations which are likely to be less disturbing These include NEOSYNEPHRIN, BENZEDRINE, PROPADRINE, PRIVINE, PAREDRINE, *etc* The dose of ephedrine is gr. ¼ to ½, and should be given in combination with a mild sedative, such as PHENOBARBITAL gr. ⅛ to ¼. Ephedrine may also be administered in a 1 per cent solution, intranasally, for hay fever and allergic rhinitis. In these conditions, however, it is advisable to restrict the use of intranasal treatment because, following primary shrinkage and relief, the patient invariably experiences a certain amount of local irritation and swelling due to secondary congestion of the mucous membrane.

f intrinsic asthma Vitamin B and vitamin B complex ave been given with suggestion of benefit in some cases f infantile eczema.

Glucose. The administration of hypertonic solutions of glucose has been thought by some to be beneficial in the treatment of status asthmaticus because it relieves local edema. In such instances we prefer to give the aminophylline in glucose of high concentration.

Aspirin. In nonsensitive aspirin cases this drug has given relief from asthma

Cocaine. This drug is used locally in nasal allergy, in a 1 per cent solution, usually in combination with epinephrine or ephedrine, in some cases of hay fever and allergic rhinitis. It is very effective but should not be employed indiscriminately because of possible habit *formation* and because patients are occasionally sensitive to cocaine or to cocaine substitutes, such as novocaine, nupercaine, etc. It is to be noted that many of the proprietary sprays sold for the relief of asthma and hay fever may contain this drug, and for this reason their use should be discouraged.

Iodides. There are few drugs that are used more universally in asthma than sodium and potassium iodide. The average asthmatic can usually tolerate fairly large doses of the drug

Sedatives and Hypnotics. Many allergic patients need some form of sedation during the acute stage of their condition Some individuals may have an idiosyncrasy or even an allergy to sedatives such as the BARBITURATES. I recall a patient who was given phenobarbital for sedation during the course of an acute attack of urticaria A short time later she developed a drug dermatitis with intense pruritus which made her quite irritable For this irritability she received more phenobarbital, with the result that her allergic dermatitis became worse. It is *important* to remember that an allergic patient may be quite sensitive to the

is at times life-saving because of its effect on the circulatory center.

Ergotamine. Ergot stimulates the sympathetic inhibitory functions and relaxes cerebral vascular spasm. This drug is used on the assumption that allergic headaches and migraine are due to edema of the meninges. The dose is 1.0 mg. of ergotamine tartrate by mouth or, if this is ineffective, intramuscularly in doses of 0.5 mg The drug should be given at the very onset of the headache. In some instances it has been found clinically valuable, especially in the symptomatic treatment of migraine and allergic headaches. Untoward effects from its administration, such as generalized pains and aches and gastric disturbances, may be relieved by the administration of atropine.

Xanthine Drugs. CAFFEINE has been frequently known to give marked beneficial results in the treatment of status asthmaticus when taken in the form of hot black coffee. THEOPHYLLINE is one of the xanthine diuretics and is frequently given in combination with ephedrine and phenobarbital. AMINOPHYLLINE is given in doses of 7.5 gr intravenously, preferably in 10 to 30 cc. of normal saline or 25 per cent solution of glucose, in cases of status asthmaticus where epinephrine seems ineffective The drug may be given rectally dissolved in distilled water or in the form of a suppository in 15-gr. doses, or it may be administered intramuscularly. It must be given slowly and may be repeated daily. It acts as a diuretic and bronchodilator. This is the explanation also for the occasional beneficial effect on the asthmatic state observed from the administration of any of the xanthine drugs.

Vitamins. There is as yet no conclusive evidence that allergic individuals are particularly deficient in vitamins, or that such deficiency has any connection with their allergic manifestations. However, the opinion of some is that administration of ascorbic acid is of value in many instances

therapy. Nonspecific therapy may involve the use of histamine Medicinal therapy indicates the use of the following: epinephrine, ephedrine, atropine, narcotics, ergotamine, caffeine, theophylline, aminophylline, vitamins, glucose, avertin, aspirin, cocaine, iodides, sedatives and hypnotics, oxygen and helium, sulfa drugs, and other miscellaneous therapeutic procedures Diet therapy includes the use of elimination and trial diets.

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DIET THERAPY

The dietetic treatment of allergic conditions includes the avoidance of foods to which the patient is sensitive, as discussed previously. Occasionally, a diet is prescribed which follows the pattern of the elimination diets included in Chapter 4. The patient is given only a few ordinarily nonallergic foods and is kept on this diet for two weeks, during the course of which he improves if his symptoms are due to the foods which have been eliminated from his menu

SUMMARY

It is evident from the foregoing that the allergic patient can be subject to extensive therapeutic procedures, some of which have a valuable and rational basis and yield desirable clinical results, while others are of less certain value and may even be dangerous. One cannot emphasize too strongly, first, the need of painstaking care and of prolonged observation and treatment of these patients, and, second, the importance of instituting allergic treatment early. The practice of delaying treatment for the allergic patient, especially the allergic child, cannot be condemned too strongly. Adequate treatment early in the disease will frequently save young hay-fever subjects from developing asthma, and those with a mild allergic eczema from developing the secondary skin complications which are so difficult to treat.

Proper treatment of the allergic patient involves prolonged and intelligent cooperation and careful observation. General measures include proper elimination, rest, elimination of foci of infection, psychotherapeutic procedures, and correction of coexisting pathology The allergic treatment proper is directed toward avoidance of causative factors. This may include changes in the patient's environment, occupation, habits, and diet. Specific hyposensitization may include treatment with house-dust extract and vaccine

6

Pollen Allergy (Hay Fever)

TERMINOLOGY AND DEFINITION
ETIOLOGY
TABLE OF DISTRIBUTION OF POLLEN IN VARIOUS PARTS OF THE COUNTRY
IMMUNOLOGY
PATHOLOGY
SYMPTOMATOLOGY AND PHYSICAL FINDINGS
DIAGNOSIS
TREATMENT
NOMENCLATURE OF POLLEN DOSAGE
CASE REPORTS
SUMMARY

TERMINOLOGY AND DEFINITION

Individuals allergic to pollen may develop paroxysmal symptoms referable to the upper respiratory tract or to the lungs In the first instance the symptoms are those of rhinorrhea, obstruction to nasal breathing, sneezing, lacrimation, and itching of the eyes and nose. In these cases the condition is referred to as hay fever When the lungs are involved the clinical condition is that of pollen asthma.

ETIOLOGY

Incidence. It is estimated that about 3 per cent of the population have hay fever A knowledge of the dates of pollination of the various trees, grasses, and weeds in different parts of the country is necessary in order to ascertain the nature as well as the cause of hay fever in those districts

The following table indicates the approximate pollen flora in various sections of the United States. The plus signs

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Season	Plant	Time of Pollination
Fall (Weeds)	Cocklebur	July-September
	Pigweed	July-September
	Ragweed	August-October

2 Southern States: Georgia, Florida, Alabama, Tennessee, Mississippi, Arkansas, Louisiana, Oklahoma, Texas

Season	Plant	Time of Pollination
Spring (Trees)	Ash	April, May
	Beech	April
	Birch	March, April
	Black walnut	December-February
	Cottonwood	April, May
	Elm	February, March
	Hickory	May
	Maple	April
	Mountain cedar	December-February
	Mulberry	May, June
	Oak	April, May
	Pecan	April, May
	Poplar	March, April
	Sycamore	May, June
Summer (Chiefly Grasses)	Bermuda grass	May-September
	Johnson grass	May-October
	June grass (Blue grass)	May September
	Lamb's-quarters	June-September
	Orchard grass	April-August
	Perennial rye	May-July
	Plantain	May-September
	Red top	June-September
	Sheep sorrel	May-July
	Sweet vernal grass	April-July
	Timothy	June-September
	Yellow dock	May-July
Fall (Grass and Weeds)	Annual sage	August, September
	Cocklebur	July-September

indicate the extent to which the pollen is present in a given district. The information is a modification of a composite obtained from various sources through the courtesy of G. A. Koelsche, M.D., of the Mayo Clinic. It may be used in conjunction with Fig. 17, A and B.

Table of Distribution of Pollen in Various Parts of the Country

1. New England, Eastern, and Central States: Maine, *New Hampshire*, Vermont, Connecticut, Rhode *Island*, Massachusetts, New York, New Jersey, Pennsylvania, Maryland, District of Columbia, Virginia, West Virginia, Kentucky, Ohio, Indiana, Illinois, Michigan, Wisconsin.

Season	Plant	Time of Pollination
Spring (Trees)	Alder	March, April
	Ash	May
	Beech	April, May
	Birch	April, May
	Cottonwood	April, May
	Elm	March, April
	Hickory	May, June
	Maple	April
	Oak	April, May
	Pine	February-June
	Poplar	April
	Walnut	March-May
	Willow	May
Summer (Chiefly Grasses)	Amaranth (spiny)	June-September
	June grass	May, June
	Lamb's-quarters	June, July
	Orchard grass	May, June
	Plantain	May-July
	Red top	June, July
	Sheep sorrel	May-July
	Sweet vernal	May, June
	Timothy	June, July

Season	Plant	Time of Pollination
	Prairie sage	July-September
	Ragweed	August-October
	Russian thistle	July-September
	Sagebrush	July-September
	Wormwood	July September

4. Rocky Mountain States: Montana, Idaho, Wyoming, Colorado, Utah

Season	Plant	Time of Pollination
Spring (Trees)	Alder	March
	Beech	April, May
	Birch	April, May
	Black walnut	March-May
	Box elder	April-June
	Cottonwood	March-May
	Hickory	April, May
	Oak	April, May
Summer (Weeds and Grasses)	Blue grass	May-September
	Cheat grass	June, July
	Foxtail	June, July
	June grass	May-September
	Lamb's-quarters	June-September
	Marsh elder	July-September
	Meadow fescue	June-August
	Orchard grass	April-August
	Plantain	May-October
	Red top	June-October
	Rye	June-August
	Sheep sorrel	June-September
	Smooth broomgrass	June, July
	Sweet vernal grass	April-July
	Timothy	May-September
	Yellow dock	June, July
Fall (Weeds and Grasses)	Burning bush	July-October
	Cocklebur	July-September

Season	Plant	Time of Pollination
	Marsh elder	August-October
	Pigweed	July-September
	Ragweed	July-October

3. Middle Western States: Minnesota, Iowa, Missouri, Kansas, Nebraska, South Dakota, North Dakota.

Season	Plant	Time of Pollination
Spring (Trees)	Beech	April, May
	Birch	April, May
	Black walnut	March-May
	Box elder	April, May
	Cottonwood	March-May
	Elm	*April*
	Hickory	April, May
	Maple	April, May
	Oak	April, May
	Summer cypress	July-October
	Sycamore	May
	Willow	May
Summer (Chiefly Grasses)	Canada blue grass	June, July
	Lamb's-quarters	June-September
	Marsh elder	August-October
	Orchard grass	*June-August*
	Plantain	May-September
	Red top	June, July
	Sheep sorrel	May-July
	Sweet vernal grass	June
	Timothy	June, July
Fall (Weeds and Grasses)	*Annual saltbush*	*July-September*
	Cocklebur	July-September
	June grass	June
	Kochia	July
	Mugwort	*July-October*
	Pigweed (prostrate and redroot)	June-September

Season	Plant	Time of Pollination
Fall (Weeds and Grasses)	Annual saltbush	June-September
	Careless weed	July-September
	Coastal sage	August November
	Cocklebur	August, September
	Mugwort	July-October
	Ragweed	June-October
	Russian thistle	June-September
	Sagebrush	July-November
	Western water hemp	July-October

6. Northwestern States: Washington, Oregon, Nevada, California (northern).

Season	Plant	Time of Pollination
Spring (Trees)	Alder (north)	March, April
	Birch (north)	April, May
	Black walnut	March, April
	Cottonwood	April, May
	Eucalyptus (California)	March
	Hazelnut	March, April
	Oak	March-June
	Olive	April
	Poplar	April
	Willow (north)	February, March
Summer (Weeds and Grasses)	Bermuda	May-October
	Broom grass	May, June
	Canary grass	April-August
	English plantain (north)	April-August
	June grass	May-September
	Lamb's-quarters	June-September
	Orchard grass	April-August
	Perennial rye (west)	May, June
	Red top	June-September
	Sweet vernal grass	April-July

Season	Plant	Time of Pollination
.	Mountain sage	July-October
	Pigweed	July-September
	Prairie sage	July-September
	Ragweed	July-October
	Russian thistle	July-October
	Sagebrush	*August-October*
	Western water hemp	July-September

5. Southwestern States: Texas, New Mexico, Arizona, California (southern)

Season	Plant	Time of Pollination
Spring (Trees)	Ash (Arizona)	March-May
	Cottonwood	February-April
	Cypress	April
	Eucalyptus	March
	Hickory	April, May
	Maple	March, April
	Mesquite	May-August
	Mountain cedar	December-February
	Oak	April May
	Olive	April, May
	Walnut (Arizona)	March-May
Summer (Weeds and Grasses)		
	Bermuda grass	May-October
	Canary grass	April-August
	Johnson grass	May-October
	June grass	June-September
	Lamb s-quarters	June-September
	Orchard grass	March-August
	Perennial rye	May, June
	Pigweed	June-September
	Plantain	May-September
	Rabbit brush (Arizona)	March, April
	Red top	June-September
	Shad scale (Arizona)	April, May
	Yellow dock	May-July

Season	Plant	Time of Pollination
Fall (Weeds and Grasses)	Annual saltbush	June-September
	Careless weed	July-September
	Coastal sage	August-November
	Cocklebur	August, September
	Mugwort	July October
	Ragweed	June-October
	Russian thistle	June-September
	Sagebrush	July-November
	Western water hemp	July-October

6. Northwestern States: Washington, Oregon, Nevada, California (northern)

Season	Plant	Time of Pollination
Spring (Trees)	Alder (north)	March, April
	Birch (north)	April, May
	Black walnut	March, April
	Cottonwood	April, May
	Eucalyptus (California)	March
	Hazelnut	March, April
	Oak	March-June
	Olive	April
	Poplar	April
	Willow (north)	February, March
Summer (Weeds and Grasses)	Bermuda	May-October
	Broom grass	May, June
	Canary grass	April-August
	English plantain (north)	April-August
	June grass	May-September
	Lamb's-quarters	June-September
	Orchard grass	April-August
	Perennial rye (west)	May, June
	Red top	June-September
	Sweet vernal grass	April-July

Season	Plant	Time of Pollination
	Timothy	June-August
	Velvet grass	May-July
Fall (Weeds and Grasses)	Burning bush	July-October
	Coastal sage	August-November
	Mugwort	July-October
	Pigweed (east)	July-October
	Rabbit bush	April, May
	Russian thistle (east)	July October
	Sheep sorrel	May-July
	Western ragweed	July-October
	Yellow dock	May-July

The foregoing table gives *only an approximate* idea of the various pollens found in the United States. Some of these pollens are more frequent hay-fever offenders than others. In some districts the list may be larger than that presented here. Obviously the clinical problem becomes quite complicated in parts of the country like California, where the fall of pollen is abundant and the number of different pollens is great One should not conclude that all the pollens enumerated above are found in every state included for each section of the country. Thus, in Pennsylvania the important tree pollen is oak; the important grasses are timothy, orchard, blue grass, red top, and sweet vernal grass The chenopod and dock group are usually not clinically important.

There are a certain very small number of hay-fever patients who do not show skin reactions to the usual pollens which are known to be prevalent in a particular district. This is especially true of certain sections of the country, such as the southeastern section of the United States and Florida These patients have seasonal hay fever which usually starts in the middle of May and lasts until the cool

weather sets in. The symptoms are typical, for they are paroxysmal and usually worse at night. The patient experiences complete relief when he changes to another district. Further study of these patients reveals that some of them may be sensitive to fungi, but there still remains a fairly large number the etiology of whose hay fever is not definitely known. In the eastern section of the country it has been established that some of the patients referred to above are sensitive to wild rice, cocklebur, marsh elder, and to a lesser extent to artemisia and the amaranth, in spite of the fact that until recently we were not accustomed to regard the pollens enumerated as common in those districts Extensive investigation has ruled out the possibility that the emanations of seasonal insects are a factor in this group of seasonal hay fever patients

Characteristics of Hay-fever-producing Pollen. Of all the pollens produced by various forms of vegetation, only a few, fortunately, are clinically important as a cause of hay fever To cause hay fever a pollen must have the following properties it must be produced in sufficiently large quantities, must contain the excitant of hay fever, must be windborne, and must be produced by a plant or grass which is sufficiently widely distributed In view of these requirements it is easily understood why a pollen such as goldenrod is clinically unimportant. Goldenrod is very conspicuous because of its color and is usually found in the neighborhood of ragweed (Figs. 18 and 19) For this reason, goldenrod has been blamed for producing hay fever. Goldenrod pollen is not sufficiently buoyant to be carried by the wind, and when it is clinically important it produces symptoms only as a result of direct contact, such as smelling. The same applies to the pollen of such flowers as roses.

Role of Climate. The severity of a given hay-fever season or of symptoms shown by hay-fever patients from day to day during the season depends largely on the amount of

State	City	Pollen (Jan – Dec)
ALABAMA	Montgomery	Tree; Grass; Ragweed
ARIZONA	Phoenix	Tree; Ragweed; Grass; Ragweed; Amaranth; Russian Thistle Salt Bush
	Kingman	Ragweed
ARKANSAS	Little Rock	Tree; Grass; Ragweed
CALIFORNIA	Northwestern	Tree; Ragweed Sage; Grass; Chenopod Salt Bush
	Southern	Tree; Russian Thistle; Grass; Ragweed Sage
	San Francisco Bay	Tree; Ragweed Sage; Grass; Dock Plantain
COLORADO	Denver	Tree; Grass; Sage; Russ. Thistle Kochia; Ragweed
CONNECTICUT		Tree; Grass; Ragweed
DELAWARE		Tree; Grass; Ragweed
DIST OF COLUMBIA	Washington	Tree; Grass; Ragweed
FLORIDA	Miami	Tree; Grass; Grass; Ragweed
	Tampa	Tree; Grass; Ragweed
GEORGIA	Atlanta	Tree; Grass; Ragweed
IDAHO	Southern	Tree; Sage; Russ. Thistle Salt Bush; Grass; Ragweed
ILLINOIS	Chicago	Tree; Grass; Ragweed
INDIANA	Indianapolis	Tree; Grass; Ragweed
IOWA	Ames	Tree; Grass; Ragweed
KANSAS	Wichita	Tree; Grass; Russ. Thistle Amaranth; Ragweed
KENTUCKY	Louisville	Tree; Grass; Ragweed
LOUISIANA	New Orleans	Tree; Grass; Ragweed
MAINE		Tree; Grass; Ragweed
MARYLAND	Baltimore	Tree; Grass; Ragweed
MASSACHUSETTS	Boston	Tree; Grass; Ragweed
MICHIGAN	Detroit	Tree; Grass; Ragweed
MINNESOTA	Minneapolis	Tree; Grass; Chenopod Amaranth; Ragweed
MISSISSIPPI	Vicksburg	Tree; Grass; Ragweed
MISSOURI	St. Louis, Kansas City	Tree; Grass; Ragweed

FIG. 17B

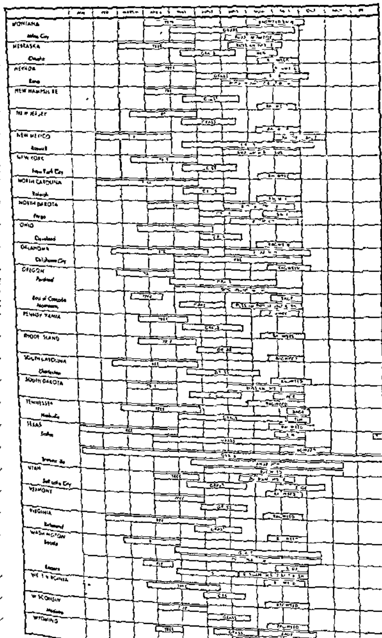

MONTANA
Miles City
NEBRASKA
Omaha
NEVADA
Reno
NEW HAMPSHIRE
NEW JERSEY
NEW MEXICO
Roswell
NEW YORK
New York City
NORTH CAROLINA
Raleigh
NORTH DAKOTA
Fargo
OHIO
Cleveland
OKLAHOMA
Oklahoma City
OREGON
Portland
East of Cascade Mountains
PENNSYLVANIA
RHODE ISLAND
SOUTH CAROLINA
Charleston
SOUTH DAKOTA
TENNESSEE
Nashville
TEXAS
Dallas
Brownsville
UTAH
Salt Lake City
VERMONT
VIRGINIA
Richmond
WASHINGTON
Seattle
Spokane
WEST VIRGINIA
WISCONSIN
Madison
WYOMING



FIG. 18. Ragweed pollen grains. Note spicules.



FIG. 19. Short or dwarf ragweed (*Ambrosia elatior*).

ollen in the air and the degree of individual sensitivity. The quantity of atmospheric pollen depends to a great extent on the prevailing climate. For example, heavy rains preceding the hay-fever season naturally aid in the growth

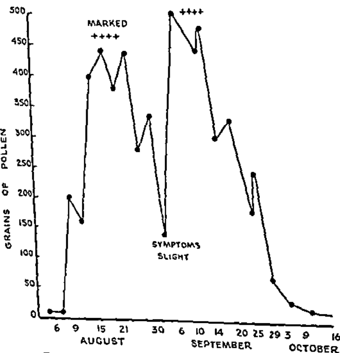


Fig 20 Ragweed pollen count (season 1943)

of vegetation and increase the abundance of pollen. Sunshine in the early morning hours helps to dry the pollen and in this way renders it lighter for wind distribution. Heavy winds help to distribute pollen and increase its concentration in the air

Pollen Counts (see Fig 20) Daily pollen counts are obtained by exposing petrolatum-covered slides to the air for

24-hour intervals and then counting the number of pollen grains per unit area. In this way a graph is plotted indicating the number of pollen grains per unit volume of air. One can foretell almost accurately, by reference to this chart, the severity of the symptoms experienced by the hay-fever sufferer from day to day. When the graph indicates a high pollen count the chances are that the patient is very uncomfortable. It is therefore important, in evaluating the effect of various forms of treatment, that there be kept an accurate daily record of the severity of the patient's symptoms and also another chart showing the relation between these symptoms and the amount of pollen fall during a given period.

IMMUNOLOGY

The immunologic considerations of hay fever have been discussed under the general heading of Immunology in Chapter 3, Allergy Hay fever is a familial or atopic form of allergy In view of this, the same principles apply to the present discussion as have been considered under the headings of heredity, antibodies, criteria for allergic diagnosis, and the mechanism of allergy production.

We do not know the nature of the hay-fever excitant in pollen. Some think it is a protein However, tryptic digestion with almost complete removal of the protein fraction does not seem to destroy the activity of the pollen There is some evidence also that it may be a carbohydrate. Investigations carried out with ragweed pollen indicate that it is a complex substance containing two demonstrable fractions, an albumin and a proteose. The degree of sensitivity to each of these two fractions differs with the individual hay-fever patient.

PATHOLOGY

The morphologic changes in the nasal mucous membrane of a patient who has hay fever are identical with those de-

scribed under Physiology and Pathology in Chapter 8, Nasal Allergy As in nasal allergy, the changes are at first reversible. Later on definite infection may supervene, giving rise to the usual characteristic findings The nasal secretion is thin, watery, and rich in eosinophils. Mucous polyps may be found.

SYMPTOMATOLOGY AND PHYSICAL FINDINGS

The hay fever patient complains of considerable nasal and ophthalmic disturbances *These consist of profuse*, paroxysmal rhinorrhea and sneezing accompanied by lacrimation and itching of the roof of the mouth, the nose, and the eyes There is noticeable obstruction to nasal breathing Some patients develop bronchial asthma toward the end of the season The nasal mucous membrane is typically allergic in appearance—swollen, boggy, and showing a pale-bluish edematous appearance. The writer has also noticed that certain "toxic" manifestations accompany severe hay-fever symptoms

DIAGNOSIS

The direct diagnosis of hay fever is easy. The condition is recognized because of its typical symptoms which occur seasonally The criteria for allergic diagnosis are present. Skin tests are positive to pollen. These include skin testing (by either the intradermal or the scratch method) and mucous membrane tests, such as the nasal (sniff) and the ophthalmic test The tests are performed to determine the exact pollen or pollens responsible for the symptoms. The results thus obtained usually match the information revealed by the history In other words, if a patient living in the eastern part of the country complains of hay fever beginning on August 15 and lasting until the first frost, the likelihood is that his hay fever is due to ragweed. The first

pollen to which he is tested and found positive is ragweed. It is also well to test the patient to all the other pollens to which he is exposed, such as grasses, plantain, and trees, because he may show in subsequent years a change from one type of hay fever to another. If he gives a positive reaction to grasses, this indicates that even though he does not have grass hay fever at present he is nevertheless a potential grass hay-fever patient. Skin tests are carried out by the intradermal or scratch technic, employing three different concentrations of pollen extract. Each dilution is 10 times stronger than the preceding one. In this way one may determine not only the offending pollen, but also to some extent the degree of skin sensitivity and the strength of dosage needed for each patient. While this does not hold good in all cases, it is sufficiently valid to warrant its use in the diagnosis of most hay-fever patients. It is very unusual for a hay-fever sufferer to fail to give a positive skin test to the pollen to which he is sensitive. The reverse is not true, however, for positive skin tests do not always mean clinical pollen allergy.

In instances where there is some doubt as to the diagnosis the ophthalmic or the nasal sniff test may be performed. The ophthalmic test consists, as indicated elsewhere, in the introduction of a drop of pollen extract in a concentration of 0.01 mg per cc. into the conjunctival sac. The nasal sniff test consists in having the patient sniff a few grains of dry pollen into the nose. A positive conjunctival reaction shows itself by the production of redness and lacrimation. A positive sniff test is manifested by the development of obstruction to nasal breathing, the appearance of swollen turbinates, rhinorrhea, and sneezing. In the testing of a patient it is important to remember that timothy pollen covers sensitivity to orchard grass, red top, and June grass. In a similar fashion, sensitivity to one of the varieties of oak tree covers the rest of the oak-tree family.

The differential diagnosis of seasonal hay fever is not too difficult The condition must be differentiated from the common cold, with which it used to be confused, and also from allergic rhinitis. The common cold does not occur seasonally, it lasts only a few days, the nasal secretion is thin and watery only at its onset, becoming thick and purulent later. The nasal secretion in the common cold is rich in polymorphonuclear leukocytes, while in hay fever the eosinophil predominates In addition, hay fever is associated with the presence of one or more of the various criteria for allergic diagnosis. Hay fever is differentiated from allergic rhinitis, which is perennial, by the positive skin tests to pollen and the periodic, seasonal history.

TREATMENT

Specific Treatment. Annual. The purpose of treatment is to reduce the severity of the patient's symptoms and if possible to prevent the development of asthma. In spite of individual preferences and variations, the general method of specific treatment is more or less uniform Increasing doses of pollen extract are given subcutaneously at weekly intervals This treatment is begun sufficiently early so that the patient receives the maximum dose at the beginning of the season. The dose is increased, provided there is no severe local reaction such as intense swelling of the arm, itching of the palms of the hands, or a more severe general or constitutional reaction such as urticaria or hay fever Should such a reaction occur the previous dose is repeated The maximum dose is then given at weekly intervals throughout the hay-fever season. Some patients do better with less dosage or no treatment during the season The tendency at present is to administer less than the maximum dose during the season. In order to avoid the necessity of repeating the entire procedure the following year, one may administer the maximum dose

after the season is over at intervals of three or four weeks, so that by the beginning of the following season the patient is receiving the maximum dose. This is referred to as the annual treatment.

Co-seasonal. Symptomatic relief may also be given by treating the patient with smaller doses when he presents himself during the hay-fever season. This is called co-seasonal treatment

The same dose of pollen extract should never be repeated if the period between treatments is more than four weeks. This warning must be heeded if constitutional re-

Table 14

TABLE OF POLLEN EXTRACT DOSAGE IN HAY-FEVER TREATMENT *

	Dosage in Terms of Mg. of Nitrogen	*Dosage in Terms of Pollen Units*
Day of Test	*No Treatment*	*No Treatment*
First	0.0001-0.1 of 0.001	10
Second	0.0002-0.2 of 0.001	20
Third . . .	0.0004-0.2 of 0.002	40
Fourth .. .	0.0007-0.35 of 0.002	80
Fifth	0.001-0.1 of 0.01	120
Sixth	0.002-0.2 of 0.01	200
Seventh	0.004-0.2 of 0.02	400
Eighth	0.007-0.35 of 0.02	800
Ninth	0.01-0.02 of 0.05	1,200
Tenth	0.015-0.3 of 0.05	1,500
Eleventh	0.02-0.2 of 0.1	2,000
Twelfth	0.03-0.3 of 0.1	3,000
Thirteenth	0.04-0.2 of 0.2	4,000
Fourteenth	0.05-0.25 of 0.2	5,000

* Schedule of doses (slightly modified) as originated by Dr R. A Cooke.

ctions are to be avoided. The prophylactic treatment is ot curative. Experience teaches that patients who have eceived treatment over several consecutive seasons may ubsequently get along well without any treatment.

In the left-hand column Table 14 indicates the dosage of pollen given in terms of milligrams of total nitrogen per cubic centimeter The right hand column indicates the dosage in terms of units. The amounts are not equivalent. A dose of 0 0001 indicates 1 cc of an extract of pollen, the concentration of which is 0 0001 mg per cc. Instead of giving 1 cc. of such a concentration, and in order to reduce the volume of injected material, one may give 0.1 cc. of an extract, the strength of which is 0 001 mg per cc. A dose of 0 001 mg of N can be given by administering 0.4 cc. of an extract, the strength of which is 0.01 mg. per cc., or 0 2 cc of 0 02 mg. N per cc. For the purpose of stability, pollen extracts may be supplied, prepared by the addition of glycerin, in such instances it is necessary to avoid giving the patient a dose containing a total volume of more than 0 3 or 0 4 cc, because the injection of glycerin is painful and when given in larger amounts may lead to the formation of a sterile abscess Therefore, instead of giving 0 7 cc of a glycerinized preparation whose concentration is 0 01 mg of N, one may give 0 35 cc of a preparation whose strength is 0 02 mg of N. It is frequently possible to administer higher doses than represented by treatment 14 in Table 14 In such instances one merely steps the dose up to 0 06, 0 07, 0 08, 0 09, 0 1, 0 12, 0 14, 0 16, 0 18, 0 2, etc.

Pre-seasonal It is well to emphasize that it is necessary to retest hay fever patients from year to year because of the possibility of a change in the degree of sensitivity. An attempt has recently been made by Loveless to gauge the pollen dosage by the titer of "blocking" antibody present According to this plan the patient receives pre-seasonal treatment consisting of seven injections in 28 days, and the

after the season is over at intervals of three or four weeks, so that by the beginning of the following season the patient is receiving the maximum dose. This is referred to as the annual treatment.

CO-SEASONAL. Symptomatic relief may also be given by treating the patient with smaller doses when he presents himself during the hay-fever season. This is called co-seasonal treatment.

The same dose of pollen extract should never be repeated if the period between treatments is more than four weeks. This warning must be heeded if constitutional re-

TABLE 14

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Second	0 0002-0 2 of 0 001	20
Third	0 0004-0 2 of 0 002	40
Fourth	0 0007-0 35 of 0 002	80
Fifth	0 001-0 1 of 0 01	120
Sixth	0 002-0 2 of 0 01	200
Seventh	0 004-0 2 of 0 02	400
Eighth	0 007-0 35 of 0 02	800
Ninth	0 01-0 02 of 0 05	1,200
Tenth	0 015-03 of 0 05	1,500
Eleventh	0 02-0 2 of 0 1	2,000
Twelfth	0 03-0 3 of 0 1	3,000
Thirteenth	0 04-0 2 of 0 2	4,000
Fourteenth	0 05-0 25 of 0 2	5,000

* Schedule of doses (slightly modified) as originated by Dr. R. A Cooke.

or two drops every three hours. Another valuable prescription is the following:

Rx Extr. Belladonna		gr. IV
Ephedrine sulfate		gr. IX
Phenobarbital		gr. IV
M. & ft. caps no. xxiv		
Sig One capsule with water every four hours if necessary		

Local eye or nasal symptoms may be alleviated by the local instillation of the following preparation:

Rx Boric acid	2.00
Epinephrine 1-1,000	15 00
Distilled water q s ad.	60 00
M & Sig Two drops in each eye or nostril every few hours if necessary.	

The hay-fever sufferer will do well to avoid drafts and wind. He should not travel through the country. Ventilation for his bedroom should be provided through a partly opened window in the next-door room. If it is imperative that the bedroom window be opened, a damp sheet should be stretched across it so as to catch the incoming dust and pollen The use of a damp gauze mask or any of the other available masks may be helpful Change of climate is effective provided it is definitely known that the offending pollen is not found at the patient's intended destination. Many resorts widely advertised as pollen-free are found on investigation to be no better than the patient's home town. The seashore offers relief only on days when the wind blows from the sea inland

NOMENCLATURE OF POLLEN DOSAGE

There are four different methods of designating the strength of a given pollen extract. All these methods are widely used because there are advantages and disadvantages

immunity is determined by passive transfer titer or by conjunctival tests. It is claimed that this form of treatment yields excellent results because it is individualized. The final word has not yet been written in this connection. In order to avoid constitutional reactions as a result of either an overdose or the entrance of pollen extract directly into a small capillary, the patient is kept waiting in the office for 20 minutes or more following treatment. Should a reaction occur it is treated in the manner described in Chapter 4.

With the discovery by Cooke and his associates of an inhibiting or "blocking" antibody which develops in the serum of pollen-treated hay-fever patients, a forward step has been made in the study of both the immunology and therapy of hay fever. Cooke found clinical improvement in ragweed hay-fever patients who received by transfusion post-treated serum obtained from other patients. Cohen has been able to develop this "blocking" antibody in the serum of sheep injected with pollen There are, therefore, great possibilities in using this information for the purpose of evaluating and perfecting hay-fever therapy.

Nonspecific Treatment. The use of air filters and air conditioning, the employment of ephedrine, neosynephrin, epinephrine, and benzedrine preparations—some to the eyes, others to the nose, or to both the eyes and nose—may be of value in the symptomatic treatment of hay fever.

During the height of the hay-fever season some patients may become acutely ill as a result of sleeplessness and intense asthma. Under these circumstances, they may experience considerable relief following hospitalization or if they are transferred to a pollen-free air-conditioned (filtered) room. For the relief of nasal obstruction and rhinorrhea the patient is given a 1 per cent aqueous solution of neosynephrin which may be used intranasally in a dose of one

units. Therefore 1 cc. will contain 20,000 Noon units. If one dilutes this 1,000 times one obtains a dilution of 1-50,000. 100 cc of 1-50,000 dilution will contain $\frac{1}{1000}$ of 2,000,000 *units or* 2,000 *units. Hence* 1 *cc. of this will* contain 20 units. In other words, 1 cc. of a 1-50,000 dilution or 0.1 cc. of a 1-5,000 dilution is equivalent to 20 Noon units, while 0.1 cc. of 1-50,000 contains 2 Noon units.

Protein Nitrogen Unit. In order to exclude nonproteins which are nonallergenic, Cooke devised the protein nitrogen unit method of dosage. In this system one unit is equivalent to 0 00001 mg. of protein nitrogen; 10,000 units is equivalent to 0.1 mg. of protein nitrogen. Hence a ragweed concentrate found to contain 0.20 mg. of protein nitrogen is the equivalent of 20,000 units of protein nitrogen. It is not possible to convert this system into the nonprotein nitrogen system

Equivalents. However, it is possible to arrive at some idea of equivalents in the case of ragweed pollen, it has been determined that one total nitrogen unit is equal to about three-quarters of a Noon pollen unit. Now a 3 *per* cent ragweed extract yields 30,000 Noon pollen units or 0 15 mg protein nitrogen per cubic centimeter or 15,000 protein nitrogen units per cubic centimeter. It would therefore appear that 30,000 Noon pollen units are the equivalent of 40,000 total nitrogen units or of 15,000 protein nitrogen units

CASE REPORTS

Case 4 Patient, female, aged 34, gave a long-standing history of both the early (spring) and the late (fall) type of hay fever She reported to the Allergy Clinic seven years ago and since that time had been receiving prophylactic treatment for both grasses and ragweed, with good therapeutic results Her *sensitivity* to grasses, both clinically and on skin testing, had become so low that grass-pollen treatment had been discontinued. The sensitivity to ragweed was diminishing gradually.

in each and no one method has as yet been universally accepted. It is therefore desirable to understand these methods because it is occasionally necessary to translate one system of dosage into the other.

Dilution Method. Some allergists prefer to employ a 1-500, 1-1,000, 1-5,000, 1-10,000, 1-20,000, 1-40,000, 1-80,000, and 1-160,000 dilution of a concentrated pollen extract. The first dose used in treatment is 0.1 cc. to 0.3 cc. of the strongest concentration which failed to give a positive skin test. Injections are then gradually increased until the maximum dose for that individual patient is reached. The concentrated extract varies with the method of preparation. It may consist of a 2, 3, 4, or 6 per cent pollen concentration. Thus, a 1 per cent could be designated as 1-100, a 2 per cent as a 1-50 extract and a 5 per cent as a 1-20.

Total Nitrogen Unit. Pollen extracts may be standardized according to total nitrogen content. The actual allergenic strength of an extract need not depend on the total *nitrogen, since that includes protein nitrogen* as well as nonprotein nitrogen. However, this method does indicate in the same extract the relative strength of various doses This concentration is expressed in terms of milligrams of total nitrogen per cubic centimeter of extract, so that a 0.01 N extract indicates a strength of a 0.01 mg of nitrogen per cubic centimeter. One total nitrogen unit = .0001 mg. of nitrogen per cubic centimeter.

Noon Unit. This is the amount of pollen allergen (active principle) contained in one millionth of a gram of pollen. In other words, one gram of pollen contains one million units If one gram of pollen, according to the Noon system, *contains 1,000,000 units, then one* may translate the Noon system into the volume percentage (dilution) method in the following manner. Dilution 1-50 has 2 Gm. of pollen per 100 cc. Hence 100 cc. of 1-50 dilution contains 2,000,000

Teaching Points

1. Early and late hay fever may be associated. Many patients sensitive to one pollen are also sensitive to some other pollen.

2. Asthmatic manifestations are not uncommon in hay fever, and occur toward the end of the hay-fever season.

3. In the annual treatment of hay fever the patient must be taught the importance of reporting at intervals not greater than one month. Constitutional reactions may occur if treatments are given at longer intervals because the tolerance is lost

CASE 6 Patient, female, aged 43, reported to the Allergy Clinic several years ago complaining of asthma and hay fever of ten years' duration The attacks of asthma had been present since childhood The hay fever was seasonal, occurring in the spring (Memorial Day to July 4), and in the fall (August 15 to the first frost). There was a strong family history of asthma. The patient was found sensitive to several foods, house dust, and pollen. Elimination of these foods and treatment with dust resulted in freedom from asthmatic attacks. She gave a positive reaction to grasses and a negative skin reaction to ragweed although
ragweed ...
toms
to rag
of gra...
e on hot, dry, windy

Teaching Points

1. More than one allergic manifestation (asthma and hay fever) may be associated in the same patient.

2. A strong familial history is present in hay-fever patients

3. Negative skin and positive "sniff" tests to pollen may be found in some patients

4. Pollen count is related to the severity of symptoms in hay fever.

Teaching Points:

1. Prophylactic pollen treatment over a period of a number of consecutive years is frequently associated with a decrease in the clinical sensitivity of a patient to that specific pollen.

2. As in all cases of allergy, the problem presented by a hay-fever patient is largely an etiologic one.

3. The seasonal occurrence of attacks of sneezing, coryza, lacrimation, and possible asthmatic breathing renders the clinical diagnosis of hay fever easy. No longer are these conditions regarded as "colds," bronchitis, sinusitis, and conjunctivitis, but the role of pollen sensitivity is readily recognized.

4. The history of the date of onset and termination of symptoms corroborated by sensitization tests makes the etiologic diagnosis.

CASE 5. Patient, male, aged 39, stated he had been subject to "summer colds" for the past 12 years. His symptoms were paroxysmal and consisted of sneezing, running nose, obstruction to nasal breathing, lacrimation, and itchiness of the eyes and nose. The onset of these symptoms was at about Memorial Day. The condition lasted until the first frost, with a let-up in symptoms between July 4 and August 15. Toward the end of the hay-fever season the patient experienced a great deal of asthmatic breathing. He stated that his brother had hay fever and a paternal grandfather had bronchial asthma

The skin tests were positive for timothy grass pollen 0.01 mg. of N per cc., and markedly positive to a mixed ragweed extract in a concentration of 0.001 mg of N per cc.

Annual prophylactic treatment was instituted with good therapeutic results The patient had influenza during the winter of 1943-1944 and therefore missed his December treatment. Because he reported three weeks later than he should have, he was given *only 50 per cent of his regular* dose of ragweed in January. Within ten minutes after receiving this treatment he developed a severe constitutional reaction.

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SUMMARY

It is estimated that about 3 per cent of the population have hay fever. This is a clinical condition caused by sensitivity to pollen. The symptoms are seasonal and paroxysmal, and include rhinorrhea, sneezing, itching of the eyes and nose, and lacrimation. In some instances asthma occurs. The incidence and the date of onset and termination of symptoms vary with different parts of the country depending on the local flora. Furthermore, climatic conditions influence the severity of symptoms in any one given district from day to day. The diagnosis is made by the history and confirmed by sensitization tests. Treatment may be pre-seasonal, co-seasonal, or annual It involves the administration of ascending doses of suitably prepared pollen extracts. The methods of estimating pollen dosage are the dilution method, the total nitrogen method, the protein nitrogen unit, and the Noon unit.

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7

Bronchial Asthma

DEFINITION
ETIOLOGY
PATHOLOGY
SYMPTOMATOLOGY
PHYSICAL FINDINGS
LABORATORY FINDINGS
DIAGNOSIS
TREATMENT
TREATMENT OF STATUS ASTHMATICUS
BRONCHIAL ASTHMA AS A SURGICAL RISK
PROGNOSIS
EXTRINSIC AND INTRINSIC ASTHMA
CASE REPORTS
BRONCHIAL ASTHMA
CHRONIC ASTHMATIC BRONCHITIS AND BRONCHIECTASIS
PULMONARY TUBERCULOSIS AND BRONCHIAL ASTHMA
BRONCHIAL ASTHMA AND HEART DISEASE
SUMMARY

DEFINITION

Little need be said here about the well known clinical characteristics of bronchial asthma Essentially, the disorder is a form of recurrent paroxysmal dyspnea characterized by prolongation of the expiratory phase, associated with wheezing and a cough which may or may not be productive

ETIOLOGY

Various etiologic factors and immunologic considerations which were taken up under the discussion of familial allergy are also applicable to bronchial asthma. The causes of bronchial asthma are the causes of allergy in general.

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is the patient's general health? The past medical and social history are also analyzed. An attempt is made finally to establish the presence of the criteria for allergic diagnosis.

One should inquire into the association of the asthmatic condition with so-called head colds, and whether or not the asthma is worse during winter than summer. Environmental influences on the asthmatic paroxysm are also important, because those which are nocturnal suggest the possibility of a source of allergic sensitivity in the patient's bedroom. Paroxysms which occur over the week-end may have something to do with certain week-end hobbies, or forms of recreation, such as horseback riding. Asthma which occurs only at the place of business suggests, of course, exposure to some occupational factor.

The presence of a persistent cough, coming on in paroxysms, with or without wheezing, especially in children, may suggest the possibility of an allergic etiology. Nocturnal dyspnea, with or without wheezing, should indicate the necessity of careful inquiry into the possible presence of cardiac disease.

The average attack of asthma is paroxysmal and recurrent. The attacks usually come in the early morning hours, waking the patient with dyspnea, choking, coughing, and wheezing. He assumes the orthopneic condition. He may hold on to the back of a chair or to a table in an effort to bring into play the accessory muscles of respiration. He becomes anxious and sometimes panicky, insisting that the windows be opened so that he may get more air. He may be found sitting in front of an open window and is rarely found lying quietly in bed. There is usually a sense of tightness across the chest. The wheezing, usually expiratory, may be audible without the use of the stethoscope. The dyspnea is expiratory. The cough is dry, hard, and exhausting. As the patient's condition improves the cough becomes

phils. When stained, especially with the Mallory technic, the basement membrane of the bronchus is prominent, hyalinized, and stains blue, having the appearance of a thick line beneath the epithelium.

In long-standing cases the following may be observed: the mucous glands in the wall become hypertrophied and are usually surrounded by an inflammatory reaction. The cartilage often shows degenerative changes There is definite thickening of the wall of the pulmonary arteries due to an accompanying sclerosis. In cases of status asthmaticus, the sections show that the lumena of the bronchi and bronchioles are plugged with dense mucus, infiltrated with eosinophils.

SYMPTOMATOLOGY

The points to be covered in the history are, first, those that are emphasized in taking a general medical history. In addition, an effort is made to elicit information of the sort outlined in Chapter 4, dealing with history taking in allergic patients. Additional factors may be mentioned as follows: inquiry is made into the date of onset and the characteristics of the first paroxysm of asthma, with special attention to the following questions. What were the accompanying circumstances? Was the condition associated with some change in the patient's occupation, environment, or habits? What is the frequency, duration, and severity of the individual attacks? Have they been sufficiently severe to necessitate calling a physician, and has it been necessary for the patient to receive epinephrine subcutaneously? If so, was the administration of the drug followed by relief? How often and how much of this drug does the patient take? Are there symptoms present suggestive of nasal infection or sinusitis or bronchiectasis? What treatment has the patient received for his condition? Does change in environment affect the patient's symptoms? Are there any house pets, plants, or sachets in the home? What

terize the disorder, and the presence of the criteria for allergic diagnosis. The clinical diagnosis is, as a rule, simple. The etiologic diagnosis is described in Chapter 4.

Differential Diagnosis. Occasionally, however, one finds it difficult to determine whether a given asthmatic condition is due to bronchial asthma or to some other condition for which it may be mistaken. One should, therefore, accept the patient's diagnosis of "asthma" very critically. After one has subjected a patient complaining of asthma to prolonged allergic studies and treatment, it is humiliating to find that the actual condition is heart disease or tuberculosis. Chevalier Jackson's dictum that "all that *wheezes* is not bronchial asthma" emphasizes this point.

VARIOUS CONDITIONS PRODUCING ASTHMATIC BREATHING. In children one must keep in mind the possibility that asthmatic symptoms may be due to foreign bodies in the bronchial tree, to enlarged tracheobronchial lymph nodes, or to an enlarged thymus. In adults, bronchial asthma must be differentiated from such conditions as paroxysmal nocturnal cardiac dyspnea, mediastinal tumor, chronic bronchitis associated with pulmonary tuberculosis, and pressure in the chest due to aneurism or foreign body. In addition to the above, proper analysis will take into consideration the following: laryngeal involvement due to spasm, inflammation or neoplasm, bronchostenosis, pulmonary atelectasis, emphysema, pressure from without the bronchial tree due to enlargement of the thyroid, and the presence of the thymus gland.

CARDIAC ASTHMA. In patients over the age of 50, especially in those who do not have a pre-existing history of asthma, a great deal of study is sometimes necessary in order to differentiate between cardiac and bronchial asthma. This differentiation is obviously important also from a therapeutic viewpoint. In bronchial asthma, difficulty in breathing is due to edema of the bronchial mucous membrane and not to circulatory failure. On the other hand, in

more productive, at first of a thick tenacious sputum which later assumes a more liquefied consistency.

In the periods between attacks, the patient feels relatively well. Exertion and upper respiratory infections will *frequently induce an attack.*

In children, the dyspnea is not as a rule very marked. There may be a persistent unexplainable cough without dyspnea and with little or no wheezing. Unlike adults, children may have a fairly high elevation of temperature during the paroxysm of asthma and for this reason the condition may be mistakenly diagnosed as bronchopneumonia

PHYSICAL FINDINGS

The physical findings in bronchial asthma are numerous sibilant and sonorous rales heard throughout the chest. The expiratory phase is definitely increased over the inspiratory phase. In advanced conditions one may elicit the findings of bronchostenosis or bronchiectasis. Emphysema may be present.

LABORATORY FINDINGS

The blood count shows a slight leukocytosis and eosinophilia. The sputum shows a preponderance of eosinophils and Curschmann's spirals. The vital capacity is reduced. As a rule laboratory examinations, such as electrocardiographic and roentgenologic findings, do not indicate cardiac involvement. The roentgenogram of the lungs shows nothing characteristic in the early stages of bronchial asthma. At a later stage in the disease, when pulmonary emphysema develops, some roentgenologic findings may be present. *Sensitization tests show positive reactions in the presence of allergy.*

DIAGNOSIS

Direct Diagnosis. The diagnosis of bronchial asthma is made on the basis of the clinical features which charac-

brought about by measures that retard the return flow of blood to the right heart, slow the heart rate, and improve the coronary circulation. The patient instinctively sits up, because the sitting posture compresses the abdominal veins and retards the return flow from the abdomen and the extremities In acute emergencies, particularly if fibrillation and congestive heart failure are present, digitalis is given intravenously. Nitrites given subcutaneously or under the tongue may be of value, because they produce peripheral and perhaps coronary dilatation as well. Such measures are of no avail in bronchial asthma, because heart failure plays no role in its production.

On the other hand, adrenalin, a drug which effectively relieves bronchial asthma, is rarely valuable in cardiac asthma. It is not difficult to understand this. Wheezy and labored breathing in bronchial asthma is, in all likelihood, the result of swelling of the bronchial mucous membrane in response to allergic irritation Adrenalin, through its vasoconstrictor action, relieves this edema, enabling the patient to breathe more easily Its use in cardiac asthma is not only of doubtful value, but is frequently contraindicated, for fatalities induced in this manner are not unknown

Cardiopulmonary Changes and Asthmatic Breathing. So far we have discussed the mechanism of production of allergic asthma and of cardiac asthma Dyspnea and wheezing respiration may also be due to cardiopulmonary changes—referred to as chronic cor pulmonale, or Ayerza's disease. We are not concerned in the present discussion with the acute or subacute phase of this condition, for neither of these produces manifestations similar to those of asthma. Acute cor pulmonale is due to sudden embolism or thrombosis of the pulmonary artery or one of its first branches, while the subacute variety is due to a gradual obstruction of the same vessels resulting from metastatic carcinomatous invasion.

cardiac asthma (or, as it is more properly called, nocturnal paroxysmal cardiac dyspnea) it is due to heart failure, particularly failure of the left ventricle.'

The left ventricle fails, either because it is not sufficiently strong to pump efficiently against the increased peripheral resistance of hypertension, or because the myocardium receives an inadequate blood supply through its narrowed coronaries. The lumena of these vessels may be narrowed also because of spasm, sclerosis, or thrombosis. Failure of the left ventricle leads to a decreased aortic (systemic) cardiac output, so that anoxemia of the respiratory and neighboring vital centers is produced. Irritation of the respiratory center gives rise to labored and embarrassed breathing which wakens the patient. Irritation of the vagus center produces bronchospasm, thus adding to the patient's discomfort. Because the left ventricle does not empty efficiently, it cannot accommodate the blood from the left auricle. Retrograde stasis and pulmonary hypertension naturally follow. If, as a result of treatment, the left ventricle recovers, or if the increased respiratory rate succeeds in producing the necessary amount of hyperventilation, the central anoxemia is relieved and the patient recovers Otherwise, the condition progresses to pulmonary edema and a fatal termination.

The aim of treatment in cardiac asthma is to reduce the irritability of the vital centers, and to improve cardiac function. The first is achieved by the use of morphine. Because this drug depresses the vital centers its beneficial effect is, as a rule, prompt and therefore dramatic. Since morphine abolishes the cough reflex, and since the vital centers play no role in the production of bronchial asthma, such results are usually not obtained from its use in this condition. Indeed, as a rule, morphine is definitely contraindicated in these instances. The second purpose of treatment in cardiac asthma—that of reducing heart failure—is

festations become evident. These include dyspnea with or without wheezing, cyanosis, hemoptysis, polycythemia, and clubbing of the fingers. Pulmonary fibrosis includes the development of progressive thickening of the blood vessels of the lungs, so that the pressure within the pulmonary arteries increases, giving rise to what is referred to as pulmonary hypertension This in turn leads to an increased load on the right heart with peripheral venous congestion, and dilatation of the right heart and of the pulmonary artery and conus There is also accentuation of the second pulmonic sound In advanced cases where most of the classic findings enumerated above are found, the condition is referred to as Ayerza's disease (chronic cor pulmonale) The clinical manifestations in the instances referred to are similar to those which may be brought on experimentally by ligation of the pulmonary artery. Postmortem examination in these patients shows a thickened right ventricle, measuring more than 5 mm.

The diagnosis of chronic cor pulmonale is made from the history, the symptoms, the findings of an enlarged right heart, prominence of the pulmonary artery and the conus, accentuation of the second pulmonic sound, and little or no enlargement of the left ventricle. The electrocardiogram shows very suggestive findings.

The prognosis in these instances must take into consideration the underlying cause. As a rule the condition runs a slowly progressive course An intercurrent lung infection may lead to death

Treatment is directed toward an alleviation of the primary condition and the treatment of the accompanying heart failure This includes complete physical rest and psychotherapy, oxygen, oxygen and helium, digitalis, sedation including opiates if necessary, reduction of salt and fluid intake, and administration of mercurial diuretics.

Routine physical examination, roentgenographic study

Chronic cor pulmonale may be due to a variety of causes One of the less frequent and less recognized causes of chronic cor pulmonale is kyphoscoliosis, where the long-standing chest deformity leads to a decrease in the functional capacity of the lungs and heart, especially to a marked reduction in lung volume, with a concomitant diminution in vital capacity. The vital capacity in many of these patients is reduced to from 30 to 50 per cent of normal The respiratory minute volume is proportionately increased, for only in this manner can these patients obtain the necessary amount of oxygen from the inspired air. Any *factor which further reduces the vital capacity of these patients*—factors such as pneumonia, respiratory depressants, and an accentuation of their deformity—will seriously interfere with oxygen absorption and lead to cardiopulmonic failure. The pressure within the pulmonary artery is increased in these instances (pulmonary hypertension) leading to hypertrophy and enlargement of the right ventricle. *This is a clinical entity well worth keeping in mind* because so many of these patients present no objective findings to indicate cardiac or pulmonary failure and are considered and treated as psychoneurotics.

Another and frequent cause of chronic cor pulmonale is due to changes in lung tissue—extensive pulmonary fibrosis resulting from long-standing bronchitis, pneumoconiosis, tuberculosis, and emphysema superimposed on *bronchial* asthma.

Primary changes in lung tissue may be due to the fact that the lungs age more rapidly than the rest of the body. This ageing process is analogous to premature arteriosclerosis involving the heart, kidneys, or brain. As a result, there occurs extensive fibrosis of the lungs so that the amount of breathing space (*vital capacity*) *diminishes The individual* has, to all intents and purposes, only one or one and a half lungs with which to breathe, so that definite clinical mani-

Vaccines. Administration of respiratory vaccines is of value.

Hyposensitization with mixtures of allergens to which the individual is sensitive. This includes house dust, orris root, feather, pollen, etc.

Removal of Infection and Nasal Surgery. In view of the fact that so many patients who have bronchial asthma have an associated paranasal sinus infection, proper and adequate management of such infections becomes very important. This may involve change of climate, local treatment, or surgery Suppuration, if present, should be properly drained. It must be pointed out, however, that nasal surgery alone, such as removal of polyps, correction of deviated septa, nasal operations both radical and conservative, is not the entire therapeutic answer to the treatment of bronchial asthma An asthmatic patient may show temporary improvement following any surgical procedure. However, if he is observed for a period of time, it is found that such operations usually do not lead to permanent relief Nasal surgery is indicated only as an accessory measure designed to promote nasal ventilation and drainage. Nasal drainage should be employed always in addition to or in association with allergic treatment If any other pathology is present it should be properly treated.

Climatic Treatment. It becomes necessary occasionally to advise an asthmatic patient to change residence to dry, warm climate in high altitude such as Arizona or New Mexico This type of change is particularly of value in chronic intractable asthmatic bronchitis associated with bronchiectasis and infection of the paranasal sinuses.

TREATMENT OF STATUS ASTHMATICUS

Definition. Status asthmaticus may be defined as a condition of severe, continuous paroxysms of asthmatic breathing over a period of days and nights As a result, the patient

of the chest, electrocardiographic studies, and sputum examinations will eliminate confusion with other conditions, such as tuberculosis or mediastinal tumors.

Chronic Asthmatic Bronchitis. There are many asthmatic patients past 50 years of age in whom the outstanding finding is the presence of infection in the bronchial tree. These patients have a chronic bronchitis associated with the asthmatic syndrome, a condition commonly referred to as asthmatic bronchitis. This is to be differentiated from the type of bronchial asthma caused by allergy to exogenous factors. Asthmatic bronchitis may have started as an allergy to exogenous factors and become complicated later by infection. The condition is characterized chiefly by a predominance of cough rather than dyspnea, although both symptoms may be present. A further complication is the development of emphysema and bronchiectasis.

TREATMENT

The reader is referred to Chapter 5 in which the treatment of allergy is discussed in detail.

Medicinal. This involves the use of such drugs as epinephrine 1-1,000, and 1-100, ephedrine, atropine, stramonium-containing powders, iodides, calcium, acetylsalicylic acid, and whiskey, also various forms of sedation.

Avoidance of Exciting Factors. This includes dietary treatment. If patients are deprived of certain foods for any length of time, vitamins should be supplied Elimination of tomatoes and orange juice from a patient's diet makes it necessary to substitute vitamin C. Other deficiencies including minerals should be supplied.

Not only is it important for the patient to avoid the specific allergens to which he is sensitive, but it is equally important for him to avoid pungent odors and fumes, such as paint, gasoline, etc., which irritate the respiratory tract and may induce an attack of asthma.

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Definition. Status asthmaticus may be defined as a condition of severe, continuous paroxysms of asthmatic breathing over a period of days and nights. As a result, the patient

gets very little sleep, is worn out because of a persistent cough and dyspnea, eats very little, is dehydrated, toxic, anxious, and cyanotic. The management of such a patient frequently becomes a serious medical problem.

Hospitalization. If at all possible, it is desirable to hospitalize such patients. Hospitalization has the advantage of effecting a complete change in environment, and thus removing the patient from the sources of his allergy, as well as from well-meaning but disturbing friends and relatives. At the same time it helps to keep him a great deal more quiet and gives him a certain amount of security.

Psychotherapy. One must not overlook the importance of psychotherapy in the treatment of status asthmaticus. These patients develop a severe anxiety and frequently become quite panicky. The physician must therefore direct part of his efforts toward reassuring an anxious patient.

Diet. Nature takes care of the patient's dietary needs. He has very little appetite and is satisfied with liquids only. As he improves, more foods are added to the diet, omitting those to which he might be allergic.

Elimination. Attention is paid to proper bowel elimination. If necessary an enema is given. Strong saline catharsis is avoided.

Medicinal Treatment. Some asthmatic patients may be epinephrine-fast. It is well, however, to try the effect of epinephrine and see what results are obtained. The following procedure may be adopted. Medication is ordered every fourth hour. Capsules of ephedrine gr. 3/8, with or without phenobarbitol gr 1/8, are given every fourth hour, such as at 8:00, 12:00, 4:00, etc. Epinephrine 1-1,000, 0.3 cc., may be ordered every fourth hour in between, that is, at 10.00, 2:00, and 6:00, etc. It is specified that if the epinephrine injection becomes due and the patient is comfortable, it may be eliminated. If the patient is nervous and irritable, phenobarbital gr. 1/4 may be given two or three times a day.

Various hypnotics may be tried to promote and induce sleep If barbiturates are not helpful, one may resort to chloral and bromides. If the patient does not get any rest from these, then recourse may be had to the administration of one ounce of ether in three ounces of olive oil by rectum Administration of ether should be preceded by a small enema and by the application of vaseline to the buttocks. Avertin has been tried. Paraldehyde may also be valuable.

·Potassium or sodium iodide is given by mouth in massive doses to the point of tolerance, or intravenously in a dose of 10 cc. of a 10 per cent solution in order to promote expectoration. Signs and symptoms of iodism must be kept in mind, such as parotitis, acneform skin rash, rhinorrhea, and gastric irritation. Continuous inhalation of steam is helpful in promoting expectoration and liquefying the bronchial mucous secretions. Aminophylline, gr. 7.5, given intravenously very slowly every day (occasionally even twice a day), may be of great value. It dilates the bronchi. It may be advisable to administer the drug in 50 cc. of 50 per cent glucose Oxygen may be administered by the Boothby mask or in a tent. In severe cases a mixture of 80 per cent helium and 20 per cent oxygen is used to advantage Some patients who are epinephrine-fast respond to the inhalation of burning asthma powder. This powder, composed of one part of stramonium and two parts potassium nitrate, may be prescribed in combination with tincture of lobelia and belladonna The patient is instructed to place a teaspoonful of the powder in a saucer, light it, and inhale the fumes; it may be prescribed and smoked in the form of cigarettes. The therapeutic effect is brought about by the atropine and the nitrite formed from the burning of stramonium and potassium nitrate Proprietary and expensive asthma powders are similar to the one described above Ammonium chloride may be given as an expectorant if the pa-

tient has an intolerance to iodides. Narcotics are studiously avoided. Morphine should not be administered. Fluids are forced, especially if the patient is dehydrated. In most instances, however, it is not desirable to force liquids because of the associated hypersecretion and edema of the bronchi. For this reason one may have to resort to tissue dehydration. This is brought about by the administration of 50 per cent sucrose intravenously, and by ordering for the patient a low sodium and an acid-ash diet. Tincture of ipecac and syrup of hydriodic acid, when administered to children, are extremely valuable as expectorants. Vomiting induces expectoration of the accumulated mucus.

In very refractory instances, if everything else fails, one may try bronchoscopy. Fortunately this procedure is not necessary very often, but there are instances where the bronchi may be filled with thick tenacious mucous plugs which cannot be removed by any other method. Bronchoscopy is occasionally also indicated in bronchostenosis and for purposes of differential diagnosis. Drainage and lavage of the bronchial tree is also recommended in chronic asthmatic bronchitis, especially when asthma is associated with advanced bronchitis or bronchiectasis. This procedure helps to dislodge the adherent mucus and in many instances gives the patient much relief.

BRONCHIAL ASTHMA AS A SURGICAL RISK

One is frequently asked to evaluate the asthmatic patient as a surgical risk. If surgery is to be done in the period between asthmatic attacks, the procedure is usually considered safe provided proper care is taken as regards the type of anesthesia and the elimination of possible drugs to which the patient may be allergic. However, occasional chest complications following major surgery in severe asthmatic patients are more frequent than in other patients. On the

whole, if surgery is absolutely essential, it may be performed. Each case must be evaluated individually.

PROGNOSIS

A discussion of the prognosis in bronchial asthma must take into consideration the chances of complete relief from future asthmatic attacks, as well as the effect of the condition on the patient's longevity. Complete and absolute freedom from asthmatic breathing is naturally more likely to occur in asthma due to known causes. In instances where the patient is found sensitive to one or two substances, and it is possible for him to avoid exposure to or ingestion of these substances, complete relief naturally follows. The results are dramatic. This is more or less true in the case of pollen asthma. However, in the so-called intrinsic asthma (vide infra), especially where the patient has had asthmatic attacks over a period of many years and secondary infection has set in, the outlook as a rule is not so good.

Fatal termination is not a common occurrence in asthma, not even in status asthmaticus, and yet it certainly occurs much more frequently in the intrinsic or infectious group of asthma than in the extrinsic cases.

With respect to relief from annoying symptoms, prognosis depends largely on the type of care which the patient receives, and on his cooperation. Where every effort is made to eliminate all possible causes, and where the condition is adequately treated and the patient cooperates properly, the outlook is fairly good. The younger the patient the better the prognosis.

The complications of bronchial asthma are pulmonary fibrosis, emphysema, chronic bronchitis, and bronchiectasis.

EXTRINSIC AND INTRINSIC ASTHMA

Asthma has been divided by Rackemann into the extrinsic or sensitive group and the intrinsic or nonsensitive

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ic disorders The allergy may be to the bacterial protein itself or, as in the case of tuberculin type of sensitivity, to the secretory products of bacterial growth However, there is no convincing evidence that constitutional reactions are obtained in allergic patients by injection of bacterial suspensions, nor is the evidence conclusive that passive transfer tests may be obtained with bacterial extracts, in a manner analogous to the passive transfer tests obtained in ragweed-sensitive patients using ragweed pollen. This inability to obtain specific positive direct skin tests, positive passive transfer tests, or constitutional reactions with bacterial extracts, in no way excludes the possibility of allergy to these bacteria. It should be remembered that during the process of preparation of bacterial suspensions or vaccines, bacterial protein may be so altered that it is unlike the original bacteria found in the body.

CASE REPORTS

Bronchial Asthma

CASE 7 Patient, a young woman, was admitted to the hospital in status asthmaticus. She had been acutely ill with asthmatic breathing for the past five days. Expectoration was scanty. The cough and shortness of breath were extremely severe and the patient had not slept for the last three or four nights There was a previous history of asthma extending over a period of ten years. There was also an associated hay-fever condition The family history was positive for allergy The dyspnea, wheezing, cough, and cyanosis were marked.

The patient was given *the usual* treatment for status asthmaticus. During the middle of the first night of hospitalization, she became extremely uncomfortable and short of breath The house physician who was substituting for the regular resident was called to see her Not being familiar with the patient's condition, he prescribed morphine sulfate gr 1/4. Shortly after that, the patient became very cyanotic and extremely *ill* It was necessary to administer

group. This is a classification to which all allergists do not subscribe. The extrinsic group is caused by contact with or exposure to substances outside of the body, such as foods, inhalants, drugs, etc. The diagnosis is made by trial exposure and by skin tests. This group is usually found in younger patients, is associated with eosinophilia, and yields positive skin tests The patient frequently improves with change in environment, such as removal to a hospital The condition as a rule is not fatal.

The cause of the intrinsic type of allergic manifestations, whether it is asthma, chronic urticaria, or vasomotor rhinitis, cannot be demonstrated as due to exposure to outside or extrinsic substances. In this group the condition results either from an allergy to substances such as bacteria found within the body, or from some unknown or little understood cause such as endocrine dyscrasia or metabolic or reflex factors. It constitutes a greater percentage of allergic disorders in individuals past 40. The condition as a rule is chronic and may be intractable. There is no eosinophilia. The skin tests as a rule are negative. The patient does not necessarily improve when removed to a hospital. It is in this type that one finds an occasional death from asthma. It must be frankly admitted that we do not as yet completely understand the exact etiology of intrinsic asthma The incidence of the condition is gradually reduced because careful study of each patient reveals allergic factors, frequently indicating that what was considered an intrinsic asthma is in reality extrinsic. It is probable that in some instances *bronchial asthma may be due to* an allergy to bacteria. There is no definite proof of the existence of such an allergy, although there is some clinical evidence which indicates this possibility.

Bacterial allergy therefore belongs to the intrinsic aller-

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Teaching Points:

1. Presence of criteria for allergic diagnosis in bronchial asthma.

2. History of clinical sensitivity corroborated by skin tests.

3. Presence of multiple allergic manifestations in same patient

4. Development of bronchial asthma as complication of seasonal hay fever indicated necessity of instituting proper treatment of hay fever early in its course

5. Association of nasal infection and bronchial asthma Such infection should be treated adequately, the purpose of treatment being to promote nasal ventilation and drainage.

6. Sulfa drugs of some value in therapy of these conditions

7. Asthmatic patients should avoid exposure to irritating fumes of gasoline and paint, which may initiate serious asthmatic symptoms

Chronic Asthmatic Bronchitis and Bronchiectasis

CASE 9 Patient, male, aged 52, gave a history of having had paroxysmal attacks of asthma for the past 15 years. During the past two or three years, the cough became productive of a thick, yellowish, purulent material. The patient expectorates about one or two cups of sputum daily. There was also a definite history of nasal involvement accompanied by postnasal drip. There was a family history of allergy There was an associated history of eczema Skin tests showed some sensitivity to a few inhalants and foods The roentgenogram of the chest showed *evidence of bron-* [illegible]

[illegible] was given intratracheally and was followed by fairly good symptomatic relief. Local nasal therapy was also instituted

helium and oxygen and aminophylline intravenously. Only after six or eight hours of extensive treatment did her condition become less critical.

Teaching Point:

DO NOT USE OPIATES IN THE TREATMENT OF STATUS ASTHMATICUS, bronchial asthma, and hay fever.

CASE 8. Patient, female, aged 38, had been receiving treatment in the Allergy Clinic of the University out-patient department for the past three years. Her present symptoms came on at the age of 23; they consisted of considerable rhinitis, sneezing, and obstruction to nasal breathing. This condition was present throughout the year but had a tendency to become definitely worse in the fall, from the middle of August to the first frost. The nasal secretion was usually thin and watery. She also stated that about five years following the onset of her nasal symptoms she experienced a great deal of difficulty with wheezy respiration, choking, shortness of breath, and cough These symptoms were likely to come on at any time of the year. She had definitely noticed that exposure to dog, insecticides, and house dust, as well as ingestion of chocolate, gave rise to severe asthma. She was also affected by paint. Her little daughter was subject to asthma.

Skin sensitization tests revealed her to be sensitive to chocolate, dog, insecticides, and several other inhalants and foods Examination of the blood showed an eosinophilia of 9 per cent. Eosinophils were also present in the nasal secretion.

Nasal examination showed the presence of considerable infection in the nose and paranasal sinuses.

On one occasion the patient developed status asthmaticus associated with a low degree of fever and the expectoration of a thick, yellow, purulent sputum The administration of sulfonamides was a valuable adjunct to therapy.

Diagnosis:

(1) Hay fever, (2) allergic rhinitis, (3) bronchial asthma, (4) chronic suppurative sinusitis.

asthmatic history associated with clinical signs and symptoms suggestive of pulmonary tuberculosis.

2 This case emphasizes the necessity of a careful physical examination, routine examination of the sputum for tubercle bacilli, and roentgenograms of the chest in bronchial asthma

3. Iodides should not be prescribed for asthmatic patients if there is any question as to the possible presence of active tuberculosis.

Bronchial Asthma and Heart Disease

CASE 11. Patient, male, aged 58, gave a history of par- [illegible]

[illegible] hypodermic for one of the attacks with good results There were some nasal symptoms. His dyspnea was very marked on exertion There was no history of an acute attack of chest pain.

Physical examination showed an elevation of blood pressure (210/105). The heart was enlarged to the left. The venous pressure was increased, circulation time prolonged, pulse 90, and the lungs presented many loud musical expiratory rales The electrocardiogram showed changes indicating myocardial involvement secondary to hypertensive heart disease and coronary artery disease.

During the period of hospitalization it was found that morphine sulfate gr. ¼ relieved the paroxysm almost immediately.

Diagnosis:

Arteriosclerotic and hypertensive heart disease, accompanied by paroxysmal, nocturnal (cardiac), dyspnea (cardiac asthma)

Teaching Points:

1. The differential diagnosis between cardiac and bronchial asthma occasionally offers a difficult clinical problem

Teaching Points:

1. Bronchitis and bronchiectasis may complicate bronchial asthma.

2. Allergy to exogenous factors is not of much importance in this type of case. The infection in the paranasal sinuses and that in the bronchial tree are important contributory factors.

3. Iodized oil therapy intratracheally has some therapeutic value in a few instances of chronic intractable asthma associated with infection; it has no value and may even be dangerous in uncomplicated bronchial asthma.

4. The proper management of such a patient involves the elimination of such allergic factors as allergic investigation may reveal to be present; also treatment of the nasal infection and of the bronchitis and bronchiectasis, the administration of expectorants, the administration of respiratory vaccine, and change of climate.

Pulmonary Tuberculosis and Bronchial Asthma

CASE 10. Patient, male, aged 38, complained of having had asthma for four years. The asthmatic attacks were typical in onset and characterized by wheezy respiration, shortness of breath, and productive cough There was a family history of allergy He had a careful and complete allergic survey two years previously but obtained no relief from allergic treatment. He said he had lost 12 pounds in the past year. There were occasional night sweats The cough was very disturbing.

Physical examination was not conclusive Temperature was normal. A few moist rales were audible at the right apex. X-ray of the lungs was suggestive of a tuberculous process in the right upper lobe. Examination of the sputum showed tubercle bacilli.

Teaching Points:

1. Chronic pulmonary tuberculosis may be associated with or complicated by asthmatic bronchitis. It is well not to overlook this possibility in any patient who presents an

Differential diagnosis must take into consideration the presence of foreign bodies, enlarged tracheobronchial lymph nodes, enlarged thymus, heart disease, mediastinal tumor, chronic bronchitis associated with pulmonary tuberculosis, and the presence of an aneurism. Cardiopulmonary changes, particularly cor pulmonale, must also be kept in mind.

The treatment of the asthmatic patient includes the principles enumerated in the management of the allergic patient. Medicinal treatment intended to give symptomatic relief includes the use of such drugs as epinephrine 1-1,000, and 1-100, ephedrine, atropine, stramonium-containing powders, iodides, calcium, acetylsalicylic acid, whiskey, and sedation.

Treatment between attacks involves the removal of foci of infection, especially treatment of infection in the paranasal sinuses, and avoidance of offending agents. The treatment of status asthmaticus is in general similar to that of the individual attacks of bronchial asthma.

The prognosis depends to a large extent on the type of asthma, the duration of the condition, and the cooperation of the patient.

Extrinsic and intrinsic asthma have been classified depending on the nature of the causative agents

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2. The cardiac basis of the attacks is established by evidence of (a) hypertension, (b) luetic aortitis, (c) coronary artery disease.

3. These patients require a great deal of careful observation and study.

4. The prognosis is, of course, much more serious in cardiac asthma than it is in bronchial asthma.

SUMMARY

The clinical manifestations of bronchial asthma consist of recurrent paroxysmal dyspnea characterized by prolongation of the expiratory phase associated with wheezing and cough.

Bronchial asthma is subject to such influences as climatic changes and seasonal variations. The occupation of the patient, his emotional stability, and the presence of foci of infection, particularly in the upper respiratory tract, also influence the frequency and severity of the asthmatic attack.

The medical investigation of the asthmatic patient includes a properly taken history, a complete physical examination, and routine and special laboratory investigation. Additional diagnostic aids such as a rhinologic examination may be necessary. The history includes a general medical as well as a special allergic history. The latter concerns itself with listing information such as family history of allergy, history of allied allergy, the association of nasal manifestations, the influence of environmental factors, the response to administration of epinephrine, and occupational influences. The physical examination must be thorough in order to rule out coexisting pathology. The laboratory investigation includes examination of the urine, a blood count, sputum examination for tubercle bacilli, and serology A roentgenogram of the chest is necessary Special examinations include rhinologic investigation and occasionally bronchoscopic, electrocardiographic, and cardiologic studies.

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coryza, vasomotor rhinitis, or hyperesthetic rhinitis. The term nasal allergy implies that the rhinorrhea and the other nasal manifestations are allergic in origin. It should not be applied unless an allergic etiology is shown to exist. It is important to emphasize this because there are a fairly large number of individuals who present symptoms similar to those of nasal allergy but in whom no allergic basis is found These instances are therefore properly labeled as hyperesthetic rhinitis, vasomotor rhinitis, etc.

PHYSIOLOGY AND PATHOLOGY

The normal physiology of the nose depends upon the following factors the normal secretion of mucus, the purpose of which is to humidify the air, the movement of this mucus by the cilia out of the sinuses and into the nasal cavities, which action helps to clean the nose, the proper functioning of the nasal blood vessels and nerves; and finally, adequate nasal ventilation and drainage. This normal physiologic function is affected adversely by such influences as infection, nasal irritation by chemical and physical agents, obstruction, and allergy As a result of such causes, certain morphologic alterations are brought about in the mucous membrane which ultimately interfere with normal function and cause clinical disturbances.

The changes in the mucous membrane in nasal allergy depend on the stage of the clinical condition. In the early or vasomotor stage, the nasal mucous membrane is bluish-gray and edematous The reaction is reversible, appearing and disappearing, depending on exposure to the offending agent Sections taken at this time show the subepithelial layer of mucous membrane markedly edematous There is eosinophilic infiltration of the tissues, with many eosinophils present in the nasal secretions As is the case in bronchial asthma the basement membrane is thickened and prominent The edema is due to increased capillary per-

8

Nasal Allergy

DEFINITION
ETIOLOGY
PHYSIOLOGY AND PATHOLOGY
DIAGNOSIS
TREATMENT
PROGNOSIS
CASE REPORT
SUMMARY

DEFINITION

Nasal allergy is an allergic condition involving the nasal mucous membrane. It is characterized by paroxysmal rhinorrhea, sneezing, nasal obstruction, and itchiness of the nose. The mucous membrane is typically pale and edematous. The discharge is thin and watery, eosinophils are found in the nasal discharge, and the other criteria for allergic diagnosis are present.

ETIOLOGY

Causative Factors. The cause of nasal allergy is a state of sensitivity of the mucous membrane Usual allergens are such inhalants as dust, orris root, animal danders, etc Foods, physical agents, and bacteria are less frequent causes. Neurogenic, psychogenic, endocrine, and metabolic disturbances are contributory factors.

Terminology and Classification. Nasal allergy may be divided into a seasonal and a nonseasonal type. The former is due to pollen and is referred to as hay fever The perennial type is variously termed allergic rhinitis, allergic

coryza, vasomotor rhinitis, or hyperesthetic rhinitis. The term nasal allergy implies that the rhinorrhea and the other nasal manifestations are allergic in origin. It should not be applied unless an allergic etiology is shown to exist. It is important to emphasize this because there are a fairly large number of individuals who present symptoms similar to those of nasal allergy but in whom no allergic basis is found. These instances are therefore properly labeled as hyperesthetic rhinitis, vasomotor rhinitis, etc.

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meability. The bogginess and edema lead to the formation of polyps, which may fill the nose and some of the sinuses, since the mucous membrane of the sinuses is a continuation of that of the nose. The mouths of the subepithelial glands become clogged so that these undergo cystic degeneration.

However, if this process persists, other more definite changes may develop, such as hyperplasia of the epithelium, which may in time lead to papillary formation. Superimposed infection brings on additional pathology. The mucosa assumes a more or less granular appearance. The purulent discharge occurs and the secretion changes from that in which eosinophils predominate to one in which there is a predominance of polymorphonuclear leukocytes. There is an increase in the fibrous tissue of the submucosa with cellular infiltration It is obvious, therefore, that the morphologic appearance and the pathology of the membrane may be varied depending on how long and how severe a condition has existed, and whether it is superimposed by a chronic or a more recent acute infectious process.

DIAGNOSIS

Direct Diagnosis. History. An adequate history involves a consideration of such factors as are brought out in Chapter 4. In addition, one must inquire specifically into the nature of the symptoms For example, if the patient has paroxysms of rhinorrhea and sneezing, usually in the morning, and these attacks are accompanied by a thin watery discharge in which eosinophils predominate, it is very likely that the condition is one of allergic etiology. Loss of sensation of smell is a frequent accompaniment of nasal allergy. It may be either temporary or prolonged

Physical Findings The physical findings are those described above. The mucosa presents the characteristic edema, and mucous polyps may be seen. Infection is not present except when it occurs as a complicating factor.

Study of Nasal Smears. The study of nasal smears is essential in every case of rhinorrhea in order to determine the presence of allergy A thin smear is made on an ordinary slide and allowed to dry The smear is then stained either with Giemsa or Wright's stain and the percentage of eosinophils is determined. Occasionally the eosinophils may not be evenly distributed and an area may be found in the slide in which large masses of cells are present. A predominance of these cells is diagnostic of allergy

Differential Diagnosis (1) Nasal allergy is differentiated from the common cold by the following in nasal allergy one finds the criteria for allergic diagnosis, the paroxysms occur more frequently and usually in the mornings, and finally nasal allergy is noninfectious

(2) Allergic rhinitis is differentiated from sinusitis by the presence of a paroxysmal history, by the characteristic appearance of the mucous membrane, the presence of an allergic history, the presence of a thin watery discharge, and the predominance of eosinophils in the nasal secretions. In nasal infections, on the other hand, one finds a mucopurulent discharge and a predominance of polymorphonuclear neutrophils in the nasal smear The purulent discharge may drain backward and is found on the posterior pharyngeal wall

In nasal allergy the mucous membranes lining the sinuses may be edematous and swollen For this reason roentgenograms of the sinuses may indicate shadows indistinguishable from those of sinusitis A great deal of care therefore must be employed in the proper interpretation of such films

It is well to point out that patients suffering with allergic rhinitis frequently refer to their condition as "sinusitis." Occasionally, symptoms of sinusitis may develop in allergic rhinitis but treatment must be *directed* toward the primary condition

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Physical Findings The physical findings are those described above. The mucosa presents the characteristic edema, and mucous polyps may be seen Infection is not present except when it occurs as a complicating factor.

polyps blocking the right nasal cavity. There is no evidence of nasal suppuration

Diagnosis

Nasal allergy (allergic rhinitis).

Teaching Points:

1. Nasal allergy must be differentiated from nasal infection

2 The appearance of the nasal mucous membrane is characteristic

3 Prolonged nasal allergy may lead to nasal infection

SUMMARY

Allergic rhinitis is an allergic condition involving the nasal mucous membranes and characterized by paroxysmal rhinorrhea and sneezing. The mucous membrane has a typical appearance and the nasal discharge is thin, watery, and rich in eosinophils The criteria for allergic diagnosis are usually present One must have a proper understanding of the use of such terms as allergic rhinitis, vasomotor rhinitis, and hyperesthetic rhinitis The condition must be differentiated from that of nasal infection. The study and treatment of the patient with allergic rhinitis follow the same general pattern as indicated under the investigation and management of allergy in general.

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TREATMENT

The treatment of the patient with nasal allergy is covered in detail in Chapter 5. It includes avoidance, diet therapy, and hyposensitization with extracts of inhalants such as house dust, etc. Occasionally treatment with histamine is effective Because many of these patients are very irritable and emotionally upset, proper attention must be paid to these factors. Rhinologic therapy involves any procedures which will help improve nasal ventilation and promote nasal drainage. It includes the use of local applications of ephedrine and related drugs, the purpose of which is to shrink the nasal mucous membrane. Correction of nasal obstructions improves nasal breathing and promotes nasal drainage. Nasal polyps are removed, and markedly deviated nasal septa are corrected Infection if present is adequately treated. The closest type of cooperation between rhinologist and allergist will assure the patient the best therapeutic results.

PROGNOSIS

In most instances of nasal allergy the prognosis is fairly good, especially if the condition has not reached the irreversible stage and there is no marked nasal infection.

CASE REPORT

CASE 12. Patient, male, aged 24, stated he had had "sinus trouble" for the past three years. His nose ran a great deal and the nasal secretion was thin and watery His nose was blocked and he sneezed frequently. These symptoms were particularly worse in the mornings. There was a family history of allergy. Exposure to house dust and the ingestion of peanuts initiated a paroxysm The nasal secretions were rich in eosinophils There was a blood eosinophilia of 8 per cent. The skin tests showed the presence of sensitivity to many allergens. The examination of the nose revealed a swollen, edematous nasal mucous membrane with several

9.

Skin Allergy (Allergic Dermatoses)

TERMINOLOGY
CLASSIFICATION
ANATOMY OF THE SKIN
VARIOUS FORMS OF ALLERGIC DERMATOSES
DIFFERENTIAL DIAGNOSIS BETWEEN ALLERGIC DERMATOSES AND OTHER SKIN CONDITIONS
LOCAL TREATMENT OF ALLERGIC DERMATOSES
CASE REPORTS
CONTACT DERMATITIS (OCCUPATIONAL)
CONTACT DERMATITIS (NONOCCUPATIONAL)
CONTACT DERMATITIS (COSMETICS)
CONTACT DERMATITIS (EASTER EGG DYE)
INFANTILE ECZEMA (ALLERGIC)
FLEXOR ECZEMA (ALLERGIC) IN CHILDREN
ATOPIC DERMATITIS (GENERALIZED)
URTICARIA AND BRONCHIAL ASTHMA DUE TO METAPHEN
URTICARIA AND ANGIONEUROTIC EDEMA
ANGIONEUROTIC EDEMA
DERMOPHYTID (FUNGUS ALLERGY)
SUMMARY

The manifestations of allergic reactions of the skin depend on the type of allergy (familial or acquired), and on the exact location of the lesion in the skin stratum Therefore, an understanding of the terminology applied to designate these clinical conditions is predicated upon a knowledge of the anatomy of the skin, and the pathology concerned in these lesions

TERMINOLOGY

A skin condition is referred to as an allergic dermatosis if it develops as a result of a specific sensitivity to a *given*

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with the offending substance, since the epidermis has no blood vessels and the allergen could not be brought to it by the circulation It should be pointed out that the lesion of contact dermatitis may be reproduced either by patch tests (that is, by exposing the skin to the causative substance), or (as in the case of poison ivy and some other agents) by ingestion External contact, while usually the method of production of the lesion, is not the only method and is not always essential. The lesion produced as a result of contact in these individuals is a vesicle. Intra-epidermal vesiculation results from swelling of the epidermal cells and the formation of fluid between them. Later in the process there may develop weeping and, finally, secondary changes, such as hyperkeratoses and lichenification, which are accompanied by hypertrophy of the various layers of the epidermis At this stage the skin appears rough, leathery, and thickened Occasionally these lesions may occur as an extension of a primary allergic involvement of the subcutaneous layer of the skin

Clinical Considerations Contact dermatitis has been called at times dermatitis venenata, an undesirable term because it indicates that the lesion is due to a toxic factor or poison, which is not the case It is in reality an allergic condition

Distribution of Lesion. The dermatitis is likely to occur on the exposed surfaces of the body, although occasionally the allergen may be carried by the hands to covered portions of the skin Those substances which are soluble in the oil of the skin, or others which can penetrate the horny layer of the epidermis and have an affinity for the epidermal cells, will more readily produce contact dermatitis For this reason various chemicals and dyes and the oily fraction of certain plants are good contactants. In this group are found instances of allergy to vegetable and plant oils, such as poison ivy and ragweed, occupational contact dermatitis

substance. There are, of course, different types of allergic dermatoses. The classification of these is based on the distribution and character of the lesions, their location in the skin stratum, their underlying immunologic mechanism, and on the tests employed for their etiologic diagnosis.

CLASSIFICATION

A. Contact dermatitis (nonfamilial or acquired)
B. Atopic or familial allergic dermatitis
   1. Infantile eczema (allergic)
   2. Flexor eczema of children
   3. Generalized atopic dermatitis (older children and adults). If psychogenic factors predominate and if the skin has undergone certain typical changes, this condition is sometimes referred to as disseminated neurodermatitis or prurigo of Besnier
C. Urticaria and angioneurotic edema may be occasionally an atopic dermatosis
D. Dermophytid or tuberculin type of allergy

ANATOMY OF THE SKIN

For the purposes of the present discussion it is sufficient to point out that the skin is composed of (1) an outer or protective layer, the epidermis, which is composed of several layers of epithelial cells and has no blood vessels, and (2) a lower connective-tissue framework which contains the blood vessels, fibro-elastic connective tissues, and fat. The skin on the flexor surfaces of the body has a richer supply of blood vessels and is thinner, and this explains the peculiar distribution of some allergic skin conditions.

VARIOUS FORMS OF ALLERGIC DERMATOSES

Contact Dermatitis. PATHOLOGY AND IMMUNOLOGY. Allergic manifestations involving the epidermal or outer layer of the skin must obviously be due to exposure by contact

with the offending substance, since the epidermis has no blood vessels and the allergen could not be brought to it by the circulation It should be pointed out that the lesion of contact dermatitis may be reproduced either by patch tests (that is, by exposing the skin to the causative substance), or (as in the case of poison ivy and some other agents) by ingestion External contact, while usually the method of production of the lesion, is not the only method and is not always essential The lesion produced as a result of contact in these individuals is a vesicle. Intra-epidermal vesiculation results from swelling of the epidermal cells and the formation of fluid between them Later in the process there may develop weeping and, finally, secondary changes, such as hyperkeratoses and lichenification, which are accompanied by hypertrophy of the various layers of the epidermis. At this stage the skin appears rough, leathery, and thickened Occasionally these lesions may occur as an extension of a primary allergic involvement of the subcutaneous layer of the skin.

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due to metals and chemicals, similar lesions due to contact with furs, dyes, leathers, cosmetics, and drugs. The condition is characterized by intense pruritus, which leads to scratching and skin trauma.

Diagnosis. This is made by the history (see Table 15) and by means of the patch tests (see Table 16) which were described in Chapter 4.

Causative Agents. A frequent cause of contact dermatitis is nail polish and mascara Nail polish contains tin oxide and some abrasive powder. It may be colorless when used for men or it may be slightly tinted. Nail enamel or liquid nail polish contains a large variety of ingredients In general, it may be stated that these consist of a body (benzoin gum or nitrocellulose film), a solvent (acetone), a spreader (amyl acetate), and a plasticizer and a dye The allergy may be to any one of these different ingredients. At this writing no safe allergen-free nail polish or enamel has as yet been devised. This type of contact dermatitis occurs usually on the face and especially on the eyelids due to rubbing and scratching.

Cosmetic Allergy. In this field one must consider many instances where contact dermatitis results from the application of other preparations to the face, to the hair, or to the skin. This includes hair dyes, hair lacquers, shampoos, and permanent-wave preparations which may produce a very severe dermatitis of the scalp and adjacent skin Hair lacquer shellac is made now from artificial resins and may cause severe contact dermatitis It would appear desirable to patch test every patient who is about to have his hair dyed in order to obviate possible serious consequences. In one instance in the writer's practice, a woman who was emotionally unstable dyed her hair. She had dyed her hair some years previously. Following this second experience she developed a severe dermatitis of the entire scalp, face,

TABLE 15

HISTORY FORM IN CONTACT DERMATITIS

Name . . . . Date . . . .
When did your present skin trouble begin? . . . . . .
Occupation . . . . . How long? . . . . . .
Does the type of work you do affect your skin? . . . . . .
Do you use Tintex, hair dye, mascara, or henna rinse? . . .
Have you any clothing made from fur, as gloves, coat trimmings, collars? . . . . . .
If so, what kind of fur? . . . . Has it been cleaned or repaired? . . . .
If so when? . . . . Does this clothing affect your skin? . . . .
Are there any plants or flowers which make your skin burn or itch or make you sneeze when you come near them? . . . . . .
How long have you lived where you do now? . . . .
Have you a flower or a vegetable garden? . .
What chemical, if any, have you used to destroy plant insects? . . . .
Have you any pet animals? . . . .
Give the names of articles used in keeping the house clean (soaps powders, cleansers, liquids, or insecticides) . . . .
What medicines, pills, or drugs do you take for headaches, indigestion constipation, as a blood purifier, or as a tonic for weakness or other ailments? . . . .
Are there any medicines which you think disagree with you? . .
What articles do you use *on your skin*, hair, beard, nails, as soap, powder shaving cream, perfume, hair tonic cosmetics, dyes, shampoo astringent cream, flesh foods, lotions, nail polish, bleach, and oil? . . . .
Do any of these affect your skin? . . . . . .
What goods hair, feathers, kapok, cotton batting or wool are the mattresses pillows, and blankets made of? .

What foods don't you eat because.
1. You do not like them? ....
2. They disagree with you? ....
Do you have overstuffed furniture? ... . Do you know what materials were used? ....
To what do you ascribe your skin trouble? .. ..
What treatment have you had for the condition, if any? . ...
....
Is the eruption on the exposed areas of the body or upon covered areas, such as the neck where the fur would rub it, etc?
. ...
Is the eruption persistent, or do you notice any appearance and disappearance connected with the wearing of particular clothing, furs, etc, or with the eating of particular foodstuffs? ....
... .
Any undue worry associated with onset of attack? ....
History of contact with·

Acids	Paint
Alkalis	Paste
Bleaches	*Photo developing*
Chemicals	Plants
Cosmetics	Plastics
Feathers	Rubbing alcohol
Flour	Salt
Fruit and fruit juices	Shellac
Fur cleaning and dyeing	Shoe polish
Furs	Soap
Hair dye	Tobacco
Ice	Toilet preparations
Lacquer (mah-jongg)	Turpentine or benzine
Leather	Vegetables
Linoleum	*Wood alcohol*
Matches	

Is eruption made worse by

Exercise	Mechanical irritation
Factory	Sunlight
Heat	Wind
Kitchen	Work

Any additional remarks? . .. .
....

TABLE 16

LIST OF CONTACTANTS EMPLOYED FOR ROUTINE PATCH TESTING *

1 Copper sulfate—1 per cent aqueous solution
2 Sodium arsenate—10 per cent solution
3 Potassium dichromate—½ per cent aqueous solution
4 Mercury bichloride—1 1,000 aqueous solution
5 Nickel sulfate—5 per cent aqueous solution
6 Novocaine—1 per cent aqueous solution
7 Metaphen—standard solution
8 Mercurochrome—standard solution
9 Nicotine salicylate—10 per cent aqueous solution
10 Tr of pyrethrum—20 per cent tincture
11 Butesin picrate—1 per cent in white vaseline
12 Resorcin—10 per cent aqueous solution
13 Quinine hydrochloride—1 per cent aqueous solution
14 Paraphenylenediamine—2 per cent in white vaseline
15 Orris root—powdered
16 Potassium iodide—25 per cent in petrolatum
17 Formalin—5 per cent aqueous solution
18 Iodoform—powder
19 Trichophytin—1 10 (Lederle)
20 Oidiomycin—1 10 (Lederle)
21 Old tuberculin—1 10
22 Para red (deep)—powder
23 Para red (light)—powder
24 Sudan III—5 per cent in mineral oil
25 Methyl orange—5 per cent aqueous solution
26 Rhus toxicodendron (Lederle) extract diluted 1·5,000 in acetone
27 Ordinary adhesive plaster

* Sulzberger and Rostenberg Jour Allergy, 6,448 1935.

and neck, and the itching and subsequent nervous manifestations became so serious that she committed suicide.

Among other cosmetics responsible for allergy are the perspiration deterrents and deodorants Formaldehyde,

alum, menthol, and camphor are the bases for most of these preparations.

Contact dermatitis in men may be due to certain types of shaving soap, brushless shaving cream, or after-shaving lotion Certain face powders may produce contact dermatitis of the face, and certain types of mouth washes may produce lesions in the mouth.

The development of contact dermatitis is obviously in no way a reflection on the toxicity of the substance employed.

Occupational dermatoses (a form of contact dermatitis) *are not at all infrequent in industry Dr. Louis Schwartz*, of the U S. Public Health Service, has written extensively in this connection Sensitivity to resins is not uncommon. It may follow the use of ointments contained in tubes lined with resins It may be found among many workers in factories where *plastics* are prepared for use in plates for artificial teeth, telephone receivers, cigar holders, varnishes, cloth finishes, cheap jewelry, stockings, steering wheels, dishes, water containers, and rubber compounds. Since urotropin and formaldehyde are constituents of plastics, they should always be employed in patch testing for such sensitivity The dermatitis in these cases usually occurs on the hands and exposed surfaces. It results from contact with the dust *which is found in the air as well as with the* material handled. In many instances the frequency and severity of the condition are reduced considerably by proper precautions such as forced ventilation, compulsory showers, protective clothing, etc.

Contact dermatitis may occur in workers employed in the manufacture of *leather*. This may be due to allergy to the various chemicals employed in the removal of hair or in the tanning process, or it may be due to sensitivity to certain dyes. Because of this, these workers are urged to wear gloves, use working clothes while in the factory, and to

take a shower before leaving work. In this connection may be mentioned instances of contact dermatitis due to the wearing of leather, such as sweatbands in hats, wristwatch straps, shoes and gloves, or a truss. It is caused either by the dye in the leather or by the various chemicals used in the manufacture of leather. The sweat usually dissolves the chemical out of the leather and produces a dermatitis; patch tests should be performed for diagnostic purposes with a piece of leather moistened with sweat or with a saline solution resembling the composition of perspiration.

Dermatitis frequently occurs in workmen employed in the *fur* industry. It is seen in those employed in fur "dressing" or fur dyeing. Of course, contact dermatitis is not uncommon among wearers of furs. It is important to remember that if a negative patch test is obtained on the skin at the point distant to the lesion, the patch test should be repeated at some place nearer the actual skin involvement. In some instances a positive reaction may thus be obtained.

Workers in the *silk* industry and those engaged in dyeing fabrics may develop contact dermatitis. Lesions may also occur from wearing dyed dresses, dress shields, clothing made of silk or rayon, or dyed socks.

TREATMENT. Every effort should be made to distinguish between a contact dermatitis due to allergy and one due to toxicity of the substance and the consequent irritation of the skin. The treatment of contact dermatitis consists in the removal of the cause wherever that is possible. In some instances change of occupation is necessary. The usual preventive measures indicated above should be adopted among workers in factories where the condition develops.

In the case of contact dermatitis to plant oil such as poison ivy, specific "desensitization" may be employed. The active principle or the allergenic oil is obtained by extracting it out of the plant with a fat solvent such as acetone or ether. The ether is evaporated and the sticky oily fraction which

remains is dissolved in a dilution of 1-100 in absolute alcohol, or it may be diluted with sterile olive oil or with almond oil.

Treatment is given either pre-seasonally or during the season. The purpose of pre-seasonal treatment is prophylactic, namely, to develop a tolerance in the individual to the oil to which he is sensitive by the administration of gradually increasing doses of the oil extract so that the patient receives the maximum dose at or about the beginning of the season. If the dermatitis has already developed, small doses are given daily or every other day, subcutaneously.

Pre-seasonal treatment begins with the subcutaneous administration of 0.1 cc. of a 1-100 dilution of poison ivy extract. The treatments are given one week apart, with successive doses of 0.1 cc. of 1-90, 0.1 cc. of 1-80, 0.1 cc. 1-70, up to the dose which elicited a positive patch test. An attempt at specific desensitization by oral administration of the powdered leaf has been made with reported therapeutic success. This is not different from the old method employed by Indians in chewing poison ivy leaves as a method of preventing poison ivy dermatitis. A more refined technic employed by Shelmire is the administration of capsules containing dilutions of the oleoresin obtained from the dried leaves diluted with corn oil. The results from many of these forms of treatment are thought to be sufficiently good to warrant their employment. Local applications are prescribed for symptomatic relief.

Atopic or Familial (Allergic) Dermatitis. Classification. This form of allergic dermatitis is familial. It includes (a) infantile eczema, (b) flexor eczema of children, and (c) allergic (atopic) dermatitis of older children and adults, referred to occasionally as disseminated neurodermatitis (prurigo of Besnier).

Pathology and Immunology. In infantile eczema the lesion is, as a rule, vesicular. It may become oozing as a result of trauma produced by scratching The allergen is brought to the skin by the hematogenous route and is usually a food, although it may be an inhalant. The shock tissues are the endothelial cells lining the skin capillaries. As a rule there are reagins present. For this reason the diagnostic test is the scratch or intradermal test and not the patch test. The reaction from this test is an immediate wheal formation Lichenification and other secondary skin changes follow later in the disease.

As the condition develops into the chronic stage and extends into or appears in childhood, it is called allergic flexor eczema of children The characteristic lesion at this time is usually a papule Hyperkeratosis and lichenification may take place Intense pruritus is the outstanding symptom and frequently leads to secondary changes in the skin and infection due to scratching Reagins are as a rule present

Atopic dermatitis or neurodermatitis observed in adults is usually an extension of flexor eczema of children and is characterized by thickening of the skin Reagins are usually present

Eczema in children cannot always be shown to be etiologically on an allergic basis, even though the immediate wheal *type of reaction* is present and even though the condition may be associated with a positive family history or positive personal history of other allergic manifestations. In other words, a *positive wheal* reaction obtained from testing such infants and children does not necessarily indicate sensitivity to respective allergens. Furthermore, they do not indicate that the eczema must necessarily be due to an allergy to those substances

Clinical Considerations Atopic or familial allergic dermatitis may occur in infants, children, and adults. Be-

cause of certain differences it is considered advisable to follow the classification and nomenclature stated above.

Distribution. In infants the distribution is as a rule limited to the face, wrists, neck, and postauricular region. In children the lesions are found particularly on the flexor surfaces of the elbows and knees, the dorsum of the wrists, the face, and the postauricular region. As the patient becomes older the dermatitis spreads, and involves practically the entire skin area. The skin of the face and neck is thickened and smooth, the lateral edges of the eyebrows are missing because of constant rubbing and scratching, the hair is thin and sparse, and the individual looks older than he actually is.

Criteria for Allergic Diagnosis. These are usually present in atopic dermatitis. Pruritus is the outstanding symptom. The diagnostic test is the scratch or intradermal test The most frequent causes are the ingestants, although inhalants may be a factor.

Etiologic Diagnosis. Atopic dermatitis found in adults is associated with definite psychosomatic manifestations. The patient is, as a rule, high-strung and emotionally unstable. Spontaneous remissions frequently occur. Occasionally there are seasonal exacerbations which are not easily explainable. Pruritus becomes a very disturbing symptom. The patient scratches and traumatizes the skin He becomes very irritable. He cannot sleep, eat, or work His whole outlook on life becomes distorted.

TREATMENT. The treatment of familial or atopic dermatitis includes local applications, the nature of which is indicated in some prescriptions included at the end of this chapter. In addition, roentgen-ray therapy is used in the symptomatic treatment of these conditions The administration of sedatives, foreign proteins, autohemotherapy, vitamins, and psychotherapy, with frequently a change in environment, are indicated. In connection with the last sug-

gestion, it should be pointed out that hospitalization brings about surprising relief from itching as well as general improvement in the patient's condition. Hospital care makes it easier to avoid exposure to the various substances to which a patient is sensitive, and the change in environment removes emotional upsets and worries.

In infantile (allergic) eczema every effort is made to keep the child free from colds and infection Diapers should be made of cotton and boiled in boric acid solution Water and soap are used sparingly, or entirely eliminated. The skin is cleaned with a detergent The arms are immobilized at the elbows by the use of pieces of cardboard padded with cotton. The same method applies to the legs. The nails are filed, the fingers are taped. Foods to which the infant or child is sensitive are removed from his diet. If the infant is breast fed the mother is warned not to eat those foods to which the infant is allergic Sobee is a good substitute for milk Sobee contains soy-bean flour, olive oil, arrowroot starch, dextromaltose, bicalcium phosphate, and sodium chloride If it is desired to increase the carbohydrate content, more dextromaltose or sugar may be added. This preparation is available either in the form of milk in cans or in the form of a dry powder to which water is added. In other instances of milk sensitization, one may use almond milk or evaporated milk or milk that has been boiled for 15 to 20 minutes In still other instances, goat milk, now obtainable in cans, may be substituted. In using restricted diets, care is exercised to supply sufficient yeast concentrate, vitamins B, C, D, as well as calcium and other minerals

The same general principles of treatment apply in the management of generalized atopic dermatitis as seen in older patients

Urticaria and Angioneurotic Edema. PATHOLOGY AND IMMUNOLOGY The characteristic lesion in this condition is

the wheal. The predominating cell is the eosinophil. The allergy is as a rule due to foods, and less frequently to inhalants. The allergen is brought by the hematogenous route to the shock tissue, which is the endothelial cell of the skin capillaries. Hence the diagnostic test is the scratch or intradermal test. In many cases of urticaria reagins are not present, and in these instances skin testing is of no value. The allergen in both allergic dermatitis and in urticaria is a water-soluble protein, and not an oil or a simple chemical as in contact dermatitis.

Clinical Considerations. Urticaria is characterized by the paroxysmal appearance of wheals which vary in size, number, and distribution. If the swellings are massive, as in angioneurotic edema, they involve the face, lips, tongue, eyes, ears, or some of the joints. The pruritus is intense and proves very disturbing to the patient, at times interfering with his work and sleep.

Treatment. The therapy of urticaria and angioneurotic edema includes the general principles laid down in Chapter 5 for the management of the allergic patient. This involves *avoidance, elimination diets, psychotherapy, symptomatic treatment with epinephrine 1-1,000, epinephrine in oil, ephedrine, belladonna, sedatives, calcium intravenously, and autohemotherapy.* The subcutaneous administration of histamine has been of some value, using histamine acid-phosphate in a dilution of 1-5,000. Beginning with 0.1 cc., the dose is increased by 0.1 cc. every week until 0.5 cc. is reached, provided a histamine reaction is not obtained.

Dermophytid or Tuberculin Type of Sensitization. Pathology and Immunology. This is an allergy to the secretory products of bacterial or fungus growth, such as tuberculin, trichophyton, monilia, and others. The lesion is inflammatory. The location of the lesion is in the deep cutis and epidermis. Upon receiving a small amount of tuberculin intradermally, a patient who has had or now has tuber-

culosis will develop a delayed local reaction in 24 or 48 hours In a similar manner, an individual who at some time in the past has had, or who now has a fungus infection of the skin, such as ringworm or trichophytosis of the feet, elsewhere on the body may develop a skin lesion commonly referred to as dermophytid. This lesion is not an infection with trichophyton, but a manifestation of skin allergy to the protein of trichophyton or its toxic products. Upon patch testing this patient with trichophytin, a positive test may be obtained Or, on intradermal testing one may elicit a delayed positive tuberculin-type of reaction The mechanism of these reactions is not readily understood Occasionally, in atopic individuals, this form of sensitization to fungi may be accompanied by reagin formation so that skin testing yields positive immediate reactions to the wheal type

Clinical Considerations. Pruritus is a very distressing symptom in fungus allergy of the skin. The diagnostic test is the patch test or the delayed intradermal test with the fungus protein. The lesion occurs at a point distant from the original infection and assumes no specific characteristics Secondary skin lesions occur late in the disease.

Treatment. Such local treatment as indicated at the end of this chapter is frequently employed. "Desensitization" with fungus extract may be of value, using trichophytin or monilia extract diluted 1-100. The first dose is 0.1 cc and is increased gradually.

DIFFERENTIAL DIAGNOSIS BETWEEN ALLERGIC DERMATOSES AND OTHER SKIN CONDITIONS

The foregoing discussion applies to the direct as well as to the differential diagnosis between the various forms of allergic dermatoses (see Table 17) In addition, however, it occasionally becomes necessary to differentiate an allergic dermatosis from such conditions as scabies or seborrheic

TABLE 17

DIFFERENTIAL DIAGNOSIS BETWEEN CONTACT DERMATITIS AND FAMILIAL (ATOPIC) DERMATITIS

Contact Dermatitis	*Atopic Dermatitis (Flexor Eczema and Generalized Atopic Dermatitis)*
Occurs on exposed surfaces of body	Distributed over face, neck, postauricular region, wrists, and flexor surfaces of the extremities
Typical lesion is a vesicle	Lesion is a papule
Causative agent usually an oil and is oil soluble	Causative agent a true antigen, and is water soluble
No criteria for allergic diagnosis	Diagnostic skin test is the scratch or intradermal test
No reagins	Reagins are present
History of contact	No history of contact

dermatitis or insect bites. Frequently, one of these two skin conditions is found together with some form of allergic dermatosis In seborrheic dermatitis one does not elicit any of the criteria for allergic diagnosis The distribution of the lesion is about the hairy portion of the skin. The skin is oily and acne is present. The lesion is pustular and the skin tests are negative.

Scabies is occasionally difficult to recognize, and it may occur simultaneously with urticaria. Its characteristic distribution and the therapeutic test help in differential diagnosis.

LOCAL TREATMENT OF ALLERGIC DERMATOSES

The local treatment of allergic dermatoses is the same as that of dermatitis of any etiology The nature of the application which is prescribed varies with the stage of the

dermatitis—that is, whether acute, subacute, or chronic. It is intended to accomplish various therapeutic purposes: to allay and soothe, to act as an astringent, to diminish the pruritus, to relieve burning, to stimulate the skin, to remove dry scaly lesions, and to soften the skin. One must not expect too much, however, from local measures unless the basic allergic cause is also discovered and removed. Furthermore, it should be remembered that because of the chronicity of the condition many of these patients are overtreated, and there is evidence that the skin is in need of a therapeutic rest, also that the allergic patient may be sensitive to the very ointment which is prescribed for the relief of his distressing symptoms. Following is a series of prescriptions employed, with some modifications, by the Department of Dermatology of the School of Medicine, University of Pittsburgh, for the treatment of dermatitis—acute, subacute, and chronic—in their respective order.

In acute vesicular, moist dermatitis

> Rx Liquor aluminii acetatis 100.00 (Burow's solution *)
> Sig Dilute one ounce with 30 ounces of water and apply as a continuous wet dressing.

Other wet dressings which are helpful in the acute stage are saturated solution of boric acid, and solution of potassium permanganate 1-10,000 dilution

In the subexudative stage where the moisture has disappeared from the surface, it is desirable to use liquor aluminii acetatis in an ointment base which absorbs water (a partially soluble water base) This ointment base may be used in conjunction with zinc paste because the zinc paste is heavier, will stick, and will absorb water

* Burow's solution should be dispensed only when clear and freshly prepared

Rx Liquor aluminii acetatis 5.00
Aquaphor 10.00
Lassar's paste (plain) (zinc paste without salicylic acid) 30.00
M. & Sig. Apply once daily for three to four days.

Lotions and liniments may also be of value in this stage. Antipruritics may be added if necessary. Calamine lotion is prescribed with or without menthol and phenol:

Rx Menthol	0.50
Phenol	0.50
Calamine	16.00
Zinc oxide	16.00
Glycerin	
Lime water ā ā q.s.ad.	180.00

M. & Sig. Apply locally.

Lotions have as a vehicle water, alcohol, glycerin, and oil Lotions may carry active antipruritic medication such as menthol, phenol, camphor, or benzocaine.

Liniments are emulsions of fatty substances in water or other liquids. These preparations are not subject to evaporation as lotions are, and spread easier than ointments. If the skin is very dry it may be well to use calamine liniment.

Rx Calamine liniment (oil)	
Menthol	0.50
Phenol	0.50
Calamine	16.00
Zinc oxide	16.00
Olive oil q.s.ad.	180.00

M. & Sig Apply locally

After the acute lesion has subsided it may be well to resort to a mildly stimulating ointment containing tar. Ointments and creams have as a base a mineral oil such as petrolatum, or an animal or vegetable oil such as lanolin,

cocoa butter, etc Lanolin can absorb water, and for this reason is suitable as a carrier for water-soluble preparations.

Rx Crude coal tar (water-washed) 2 00
Liq alum acetatis 5 00
Lanolin or aquaphor 10 00
Lassar's plain zinc paste q s ad. 30.00
(No salicylic acid)
M. & Sig Spread on thick. Bandage. Avoid soap and water and use oil for cleansing

In the more chronic stages one may employ the following ointment

Rx Crude coal tar (water-washed) 30 00
Zinc oxide 30 00
Lanolin or aquaphor 60 00
Petrolatum (white) ā ā 60 00
M & Sig Spread on thick Bandage. Avoid soap and water and use oil for cleansing.

At the stage where the dermatitis has visibly subsided but the *pruritis* persists, the following antipruritic application may be employed

Rx Benzocaine 2 00
Ung rosae
Aquaphor
Aq calcis ā ā q s ad . 100.00
M & Sig To be applied as fine film.

In mild chronic patchy eczema where it is desirable to use a detergent as well as a mildly stimulating and antiseptic application the following may be employed.

Rx Menthol 0 25
Phenol 1 00
Liq. carb detergens . . 5 0
Vanishing cream 100.00
M & Sig. Apply locally

The above prescriptions are examples of what may be employed for the relief of local symptoms in allergic

Rx Liquor aluminii acetatis	5.00
Aquaphor	10.00
Lassar's paste (plain) (zinc paste without salicylic acid)	30.00
M. & Sig. Apply once daily for three to four days.	

Lotions and liniments may also be of value in this stage. Antipruritics may be added if necessary. Calamine lotion is prescribed with or without menthol and phenol·

Rx Menthol	0.50
Phenol	0 50
Calamine	16.00
Zinc oxide	16 00
Glycerin	
Lime water ā ā q s ad	180 00
M. & Sig. Apply locally	

Lotions have as a vehicle water, alcohol, glycerin, and oil. Lotions may carry active antipruritic medication such as menthol, phenol, camphor, or benzocaine

Liniments are emulsions of fatty substances in water or other liquids. These preparations are not subject to evaporation as lotions are, and spread easier than ointments. If the skin is very dry it may be well to use calamine liniment:

Rx Calamine liniment (oil):	
Menthol	0 50
Phenol	0 50
Calamine	16.00
Zinc oxide	16 00
Olive oil q s ad	180 00
M. & Sig. Apply locally	

After the acute lesion has subsided it may be well to resort to a *mildly stimulating ointment containing tar* Ointments and creams have as a base a mineral oil such as petrolatum, or an animal or vegetable oil such as lanolin,

the week-ends when the patient was not working Patch tests corroborated the diagnosis of sensitivity to these substances

Teaching Points:

1. This is a form of allergic occupational dermatitis due to contact.

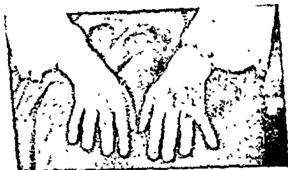


Fig 21 Contact dermatitis (occupational) in barber due to allergy to shampoos and face powder.

2 The skin lesion results from a specific sensitiveness of the outer layers of the epidermis

3 The dermatitis occurs on the exposed surfaces, but occasionally may be carried by the hands to any part of the body

4 Treatment includes the local application of antipruritics and astringents, the avoidance of skin irritation by soap and water, and the elimination of offending agents from the patient's environment.

5 One must differentiate between the toxic and the true allergic type of contact dermatitis. The term dermatitis venenata has been applied to this condition improperly because it is not the result of toxic action on the skin but is due primarily to an allergy.

dermatitis. In addition to these applications, the following also should be mentioned:

Powders may be used in the socks or shoes to protect the skin of the toes from further irritation and maceration in dermatitis of the feet. Boric acid, zinc oxide, alum, and talc are examples of powders used to soothe or disinfect such local areas.

Extensive generalized dermatitis, acute, or subacute, especially if associated with pruritus, is benefited by the use of oatmeal, starch, or bran baths.

Roentgen-ray therapy is resorted to in selected cases under careful supervision.

The patient should be instructed to avoid soap and water. Removal of encrusted scales and previously applied preparations may be effected by the use of oil or creams, but care should be exercised not to irritate the skin. Wet dressings dissolve and remove crusts, prevent itching, and allay inflammation. They are applied hot or cold as the case permits. In chronic dermatitis, sulfonated oil may be used as a detergent.

It is also to be noted that many of the clinical pictures are often masked by previous medication so that the skin is irritated or the primary lesion may even be obliterated. At any rate, local applications may lead to partial involution or to aggravation of the original condition. At times it is necessary to give the patient a complete rest from all local medication, and in this manner relieve the skin of irritation.

CASE REPORTS

Contact Dermatitis (Occupational)

CASE 13. (See Fig. 21.) Patient, male, aged 49, a barber, had been troubled with a recurrent vesicular dermatitis of both hands for the past four years. This condition was associated with marked *pruritus* and was made worse by handling shampoos and face lotions. It was relieved over

Contact Dermatitis (Nonoccupational)

Case 14. (See Fig. 23) Patient, a young girl, gave a history of a recurrent, seasonal, vesicular dermatitis occurring

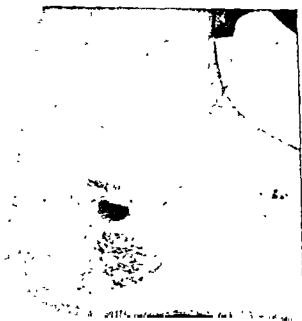


Fig 23. Poison ivy dermatitis (contact dermatitis, vesicular)

on the exposed surfaces of the body, especially on the hands and ankles There was extreme itchiness. Patch tests were positive to poison ivy

Teaching Points

1 This type of contact dermatitis is due to an allergy to the oily fraction of the poison ivy plant. It is similar to ragweed-oil dermatitis or to any other plant dermatitis. It occurs seasonally The lesion is vesicular.



Fig. 22. Contact dermatitis (occupational) due to allergy to rubber in face mask, in a patient working in a large defense plant where dust is a hazard. This condition cleared up entirely by avoidance of exposure.

Contact Dermatitis (Nonoccupational)

CASE 14. (See Fig. 23) Patient, a young girl, gave a history of a recurrent, seasonal, vesicular dermatitis occurring



FIG. 23. Poison ivy dermatitis (contact dermatitis, vesicular).

on the exposed surfaces of the body, especially on the hands and ankles There was extreme itchiness Patch tests were positive to poison ivy

Teaching Points:

1. This type of contact dermatitis is due to an allergy to the oily fraction of the poison ivy plant. It is similar to ragweed-oil dermatitis or to any other plant dermatitis. It occurs seasonally. The lesion is vesicular.

2. Prophylactic treatment is as a rule effective. It may be carried out by the preseasonal subcutaneous administration of an extract of the oily fraction of the offending plant, or by the oral administration of capsules of the active principle. Occasionally, symptomatic relief is obtained by the

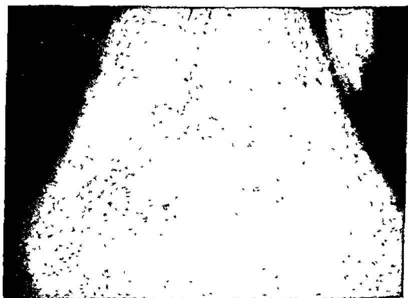


Fig. 24. Contact dermatitis to cosmetics (hair shampoo). Involvement of back of neck, face, and forearms. Positive patch test to nail polish and germicide soap.

administration of small repeated doses of a solution of plant oil during the season.

Contact Dermatitis (Cosmetics)

Case 15. (See Fig 24.) Patient, a young woman, had presented a severe vesicular dermatitis of the face, neck, upper back, and forearms for the past eight months She was employed in a shoe store but patch tests with various leathers and dyes were negative. She gave a marked positive patch

test, however, to nail polish and germicide soap Complete recovery followed avoidance of the nail polish and soap

Teaching Points:

1. This case is presented as an example of a group of contact dermatitis due to cosmetics such as deodorants, nail polish, nail dye, nail-polish remover, face powders, per-

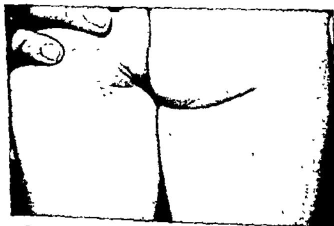


Fig 25 Contact dermatitis to toilet-seat paint and varnish in child.

fumes, shampoos, hair dyes, etc. The newer polishes are nitrocellulose lacquers Lacquer removers, especially acetone or ethyl acetate, are varnish removers.

2 This type of contact dermatitis is not uncommon It usually occurs on the face, especially on the eyelids, due to rubbing

Contact Dermatitis (Easter Egg Dye)

Case 16 A child, aged 4, presented a history of flexor eczema (dermatitis involving the elbows, knees, face, and neck) since infancy There was a strong family history of allergy The blood showed an eosinophilia. The allergic

survey and intradermal tests revealed sensitivity to several foods. Allergic treatment resulted in complete disappearance of the eczema. Six months later the patient developed an extensive vesicular dermatitis involving the hands, forearms, and face. The history elicited the information that the child had been painting Easter eggs with dyes that were prepared in the form of matches. Investigation revealed that the colors used in the matches were oil blue G (alkylaryl-amino-anthraquinone); oil red N-1700 (diazo dye belonging to the tolyl azo-zylyl azonaphthol family); oil orange 7078 (monazo dye of the phenyl azonaphthol group), and oil yellow. In addition, there was a small amount of ordinary commercial wax and sulfonated castor oil.

Teaching Points:

1. Intradermal tests with these dyes were negative, as was to be expected, since the allergy in this patient is limited to a sensitivity of the epidermis only. Patch tests, however, gave a positive reaction to red and orange but no reaction to the wax, castor oil, or other dyes.

2. Local symptomatic treatment and absolute avoidance of these dyes brought about complete relief.

Infantile Eczema (Allergic)

CASE 17. (See Figs. 26 and 27.) Patient, male, aged 2, had had eczema since birth. The lesions were at first vesicular and later became papular. For the first six months following onset, the dermatitis occurred on the face, wrists, and postauricular region Later it spread to the flexor surfaces of the elbows and the popliteal spaces. There was severe pruritus leading to continuous scratching which caused considerable skin trauma and at one time caused secondary skin infection. The skin was becoming thick and leathery. There was also a history of paroxysmal attacks of asthmatic breathing induced often by exposure to wool. The child lost his voice following the ingestion of potatoes, peas, chicken, and eggs Playing with stuffed toys induced a paroxysm of asthma. The blood count showed an eosinophilia. Intradermal tests were positive for many foods and some



FIG. 26 Infantile eczema in a two-year-old boy dating to birth and associated with hay fever and bronchial asthma.



Fig. 27. Flexor eczema in same patient as shown in Fig. 26.

inhalants Change in environment (hospitalization) and dietary treatment brought about marked improvement.

Teaching Points:

1. The distribution of atopic dermatitis in infants is as described above. As the child becomes older, the lesions are found mostly on the flexor surfaces of the elbows and knees, on the face and neck, and occasionally on the wrists.

2. The characteristic lesion in infancy is a vesicle. The characteristic lesion in childhood is a papule. In childhood, the condition is called flexor eczema of allergic origin.

3. As the dermatitis becomes more and more chronic, there appear secondary skin changes—the skin becomes thick and leathery due to lichenification and hyperkeratosis

4. The characteristic symptom is pruritus.

5. Severe nervous manifestations also develop

6. The treatment consists in the elimination of the offending factors, prevention of scratching and skin trauma, local applications, and sedation

Flexor Eczema (Allergic) in Children

CASE 18 Patient, male, aged 12, had had an eczema for the past six years At first it involved the face and dorsum of the wrists The dermatitis spread to other parts of the body so that for the past two years it involved the face, the anterior surface and the sides of the neck and the flexor [illegible] ular [illegible] pro- [illegible]

Teaching Points

This case is presented to illustrate the distribution of allergic eczema in older children, the nature of the lesion (papule), and the secondary skin changes brought about through delay and neglect in the early treatment of such conditions

Atopic Dermatitis (Generalized)

Case 19. (See Figs. 28 and 29.) Patient, female, aged 29, stated she had been troubled with her skin all her life. This condition began in childhood, at first involving the face,

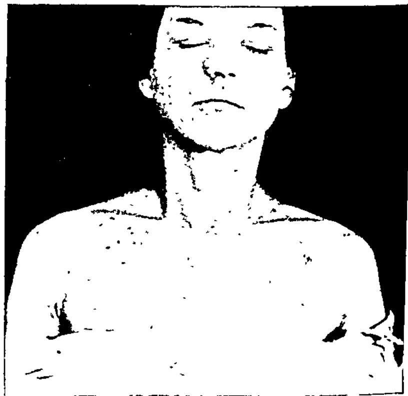


Fig. 28. Generalized atopic dermatitis in young woman. Note marked secondary skin changes.

the bend of the elbows, and the region back of the knees. It was accompanied by very severe itching and, over a period of years, began to involve the face, sides and anterior surface of the neck, the upper parts of the chest, thighs, and other parts of the body. Because of the itching, this condition was intolerable, and was particularly worse at night when under warm blankets, so that she had been sleepless

for months. It had been usual for her to awaken after one or two hours' sleep because of severe pruritus

There was a strong family history of allergy. Her little girl had eczema. The patient herself had hay fever during



Fig. 29. Same patient as shown in Fig. 28

the month of June, at which time there was considerable associated asthma In addition to these conditions, she had had a great deal to contend with because of financial and domestic situations She had noticed a definite sensitivity to chocolate and eggs, the ingestion of which aggravated her skin condition.

Examination revealed evidence of a dermatitis involving the flexor surfaces of the elbows, knees, anterior chest, anterior surface and sides of the neck, and also the face and back. The skin showed evidence of scratching and in some places of secondary infection. There was lichenification and excoriation of the skin, which had assumed a smooth, dry, shiny surface. The hair was thin and the lateral edges of *the eyebrows were rubbed off. Skin sensitization tests* showed this patient to be markedly sensitive to pollen, house dust, and certain foods, particularly chocolate and chicken.

Treatment consisted in the elimination of those foods to which the patient was sensitive, elimination of soap and water, the use of olive oil, and a detergent instead of soap, *administration of sedation at night, and psychotherapy.* With such treatment her skin responded and in the short space of a few months there was considerable improvement in her condition.

Teaching Points:

1. Universal, generalized distribution of atopic dermatitis.

2. Characteristic presence of smooth shiny skin and thin sparse hair.

3. *Secondary and associated psychogenic disturbances in* this condition and their importance in connection with the management of these patients.

4. *Long-standing, pre-existing and usually neglected allergic* flexor eczema in infancy and childhood leads to atopic dermatitis.

Urticaria and Bronchial Asthma Due to Metaphen

CASE 20. Patient, male, aged 46, was first seen five years before, when *he gave a history of bronchial* asthma of ten years' duration. Occasionally there would be a mild attack of urticaria. There was no family history of allergy. Epinephrine would give him symptomatic relief. A blood smear showed an eosinophilia. Allergic survey and intradermal tests revealed the presence of sensitivity to several inhalants

(feathers, orris root, and the like) and foods. Allergic treatment rendered him completely symptom free for about two years, after which period he returned to the clinic and gave

emergency hospital, where it was dressed after the application of metaphen. Within a half hour after this application a very severe attack of asthma developed, which lasted practically the entire night in spite of the administration of repeated injections of epinephrine.

A week later, when the finger was dressed with untinted metaphen, no reaction occurred This was repeated two days later with the same results At this time scratch tests and intradermal tests with both the tinted and the untinted metaphen were negative, but following the tests with the tinted metaphen, and ranging from a half hour to three hours after the tests were performed, a very severe attack of asthma developed which lasted practically the entire night Patch tests performed with both the tinted and the untinted metaphen were negative. After the patch test was performed with tinted metaphen, an attack of asthma developed. No such attack resulted from the patch test performed with the untinted product.

Information received from the Abbott Company states that the dye employed in metaphen is orange I. The dye is also called tropeolin 000 No. 1 and alphanaphthol orange. Chemically it is sodium azo alphanaphthol sulfanilate ($C_{16}H_{11}N_{2}O_{4}SN_{a}$) Scratch tests and intradermal tests were then performed with the dye alone (dilutions of 1 1,000 and 1 100) and a negative skin reaction occurred Several weeks later, after all symptoms disappeared, an area on the arm the size of a silver dollar was painted with the orange dye Two hours after the arm was painted a severe attack of asthma developed accompanied by generalized hives These lasted over a period of about ten hours, necessitating the frequent administration of epinephrine The procedure was repeated with exactly the same results several days later. It is interesting that when his left arm was painted with the orange dye, large hives and a massive swelling accompanied by itching, which lasted for a period of 48 hours,

developed on the right arm at the point where the scratch test was done several days previously with the tinted metaphen. Complete avoidance of exposure to the tinted metaphen resulted in complete relief.

Teaching Points:

1. The allergy presented by this patient is one that involves a sensitivity of the dermis (urticaria) and the mucous membrane of the bronchi and bronchioles (bronchial asthma).

2. It illustrates the nonantigenic nature of dyes as shown by the absence of demonstrable antibodies (reagins), for this patient gave a negative scratch and intradermal skin test as well as a negative passive transfer to the dyes to which he is no doubt allergic.

Urticaria and Angioneurotic Edema

CASE 21. (See Fig. 30.) Patient, female, aged 17, gave a history of paroxysmal attacks of hives extending over a period of three years. These attacks were typical of urticaria and were accompanied by intense itching. The paroxysm causing her to seek treatment had continued for three weeks, involving practically all parts of the body. It came on about the time of final examinations in school. The paroxysm was always worse during menstrual periods. The skin was very sensitive, so that even mild stroking would produce welts (dermographia). There was a positive family history of allergy. The blood count showed an eosinophilia. There was evidence of skin sensitivity to many allergens.

Teaching Points:

1. Recurrent intractable urticaria may prove to be a seriously disturbing condition. The patient is unable to eat, work, or sleep, is irritable, and loses weight.

2. A certain percentage of instances of generalized urticaria is allergic in origin, as evidenced by the presence of criteria for allergic diagnosis. The specific etiologic diag

nosis is based on the history, on elimination diets, and on skin testing

3. Treatment includes the avoidance of causative factors, improvement of the general health of the patient, and attention to psychogenic and emotional factors. These frequently cause, accompany, contribute to, or result from severe urticaria



Fig 30 Generalized intractable urticaria in young girl

4 The use of sedatives, adrenalin 1-1,000, adrenalin in oil, and nonspecific agents, such as histamine, calcium, chloride, and autohemotherapy, may be of value.

5 In more severe instances, the patient should be hospitalized, thus affording a complete rest and change in environment

Angioneurotic Edema

Case 22 (See Fig 31) Patient, an elderly male, presented marked swelling of one-half of the tongue This condition

had persisted for two days, and at the onset the tongue wa so swollen that it protruded from the mouth and could no be retracted. He could never take eggs or peanuts. The in gestion of either of these foods would produce sever



Fig. 31. Angioneurotic edema of tongue due to allergy to eggs and peanuts. Note marked swelling of left half of tongue.

asthma, hives, or marked swellings of the lips and tongue. There was a positive family history of allergy. The condition responded to the administration of adrenalin.

Teaching Points:

1. Massive angioneurotic edema may have an allergic cause. The diagnosis is made in a manner similar to that employed in the diagnosis of urticaria.

2. The immediate treatment involves the administration of epinephrine 1-1,000.

Dermophytid (Fungus Allergy)

CASE 23. Patient, male, aged 28, presented an erythematous, scaly dermatitis of both hands and forearms. This condition had been present for six years. It was accom-



FIG 32 Dermographia: 21-year-old girl who presents severe urticaria and angioneurotic edema. Mechanical irritation of skin, such as stroking or even light scratching, causes wheals to arise.

panied by severe pruritus, causing restlessness and sleeplessness He was extremely self-conscious and embarrassed because of this skin ailment He stated he had had "athlete's foot" several years ago. There was still some dermatitis of his toes Scrapings from the lesions on the hands failed to reveal evidence of fungi Intradermal testing gave a marked, positive, delayed (tuberculin-like) reaction to Trychophyton and Monilia

Teaching Points:

1. This is an instance of allergy to the secretory products of Trychophyton and Monilia. The fungus infection on this patient's feet sensitized the individual to the fungus proteins and secretions so that subsequent exposure brought about the dermatitis of his hands. This type of fungus allergy is commonly referred to as a dermophytid.



Fig. 33. Angioneurotic edema of eyes due to ingestion of eggs.

2. Treatment consists in the application of such local therapy as the nature of the dermatitis indicates Since no fungus infection exists, there is no need for fungicides.

3. In some instances, desirable results may be obtained by "desensitization" with increasing amounts of an extract of the causative fungi.

4. Psychotherapy also has a place in the management of these patients.

SUMMARY

The term allergic dermatoses is applied to designate all types of skin allergy. It includes (a) contact dermatitis, (b) atopic or familial dermatitis, (c) urticaria and angioneurotic edema, and (d) allergic dermatitis due to an allergy to

fungi and referred to as dermophytid. Atopic dermatitis includes a familial dermatitis of allergic origin found in infants and children and referred to as flexor eczema, and a similar dermatitis found in adults but distributed over the entire body and referred to as atopic dermatitis of adults or neurodermatitis.

An understanding of the anatomy of the skin is essential to a proper interpretation of the location and nature of the lesion in each of the above forms of allergic dermatoses. The pathology and immunology of these differ. In contact dermatitis the involvement is restricted to the epidermal layer of the skin. The lesion is a vesicle and results from contact. Secondary skin changes may occur later in the disease. The diagnostic test is the patch test. In atopic dermatitis the lesion is in the epidermis, is inflammatory in nature, and consists of a papule. The shock tissue is the endothelial cell lining of the skin capillaries. Reagins while absent in contact dermatitis are present in atopic or familial dermatitis. For this reason, the diagnostic test is the intradermal or scratch test. In urticaria the characteristic lesion is the wheal, the predominating cell is the eosinophil. The diagnostic test is the scratch or intradermal test when reagins are present. In the tuberculin or fungus type of skin involvement the allergy is to the secretory products of bacterial or fungus growth. The lesion is inflammatory and located in the cutis. This form of sensitivity is predicated on the presence of previous infection with the organism.

Clinical considerations involving allergic dermatoses vary with the type in question. In contact dermatitis one must keep in mind sensitivity to vegetable and plant oils, cosmetics, and occupational factors due to metals, chemicals, furs, dyes, leathers, drugs, etc. The treatment of these patients involves complete avoidance as well as local treatment. Occasionally special "desensitization" by oral or ...

Teaching Points:

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podermic administration of the offending extract (poison ivy) is indicated.

The etiologic diagnosis and treatment of atopic dermatitis and urticaria are practically the same as in any other allergic condition. The management of the patient presenting a dermophytid involves an accurate etiologic diagnosis This is made by intradermal testing with fungi. Occasionally specific desensitization is of value.

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Serum Allergy

GENERAL CONSIDERATIONS
TYPES OF SERUM REACTIONS
DIAGNOSIS OF SERUM ALLERGY
RISKS EXPECTED FROM SERUM ADMINISTRATION
EFFICACY OF REACTION-AVOIDING PROCEDURES
CASE REPORT
SERUM ATOPY (FAMILIAL)
SUMMARY

GENERAL CONSIDERATIONS

Following the administration of a foreign serum, an individual may or may not give evidence of a reaction. The chances are, however, that he will, for such a reaction occurs in a fairly large percentage of people. The rapidity of the onset and the intensity of the reaction depend not only on the mode of administration of the serum (subcutaneous, intramuscular, or intravenous), but also on the type and amount of serum employed and the presence and nature of an allergy to serum Because these reactions may prove serious and at times even fatal, it is important to understand them

TYPES OF SERUM REACTIONS

The reaction which a patient develops as a result of the injection of foreign serum, such as horse serum, may be of three different types (a) Ordinary serum sickness, (b) accelerated (acquired) serum reaction, and (c) familial (atopic) serum allergy It is important to understand the basis for this classification in order to obtain a clearer view of the problems which are involved

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Ordinary Serum Sickness. Within two to 14 days following the administration of a foreign serum for the first time, a patient may develop a reaction characterized by fever, skin rash (usually urticarial), joint pains, and edema. The joint manifestation may be the only symptom. The joints may be large, swollen, tender, red, and painful due to an actual local inflammatory condition. The sedimentation *rate is normal. The skin test usually becomes positive for* horse serum in about eight to 14 days following the primary injection of the serum. Leukopenia accompanies the early stages of this reaction. Eosinophilia is usually not present.

Ordinary serum reaction occurs in about 40 per cent of cases when the serum is given subcutaneously, and in about 75 per cent of cases when it is given intravenously. Heredity is not a factor. The mechanism involved in bringing about serum sickness is not clearly understood. So far there is no distinct proof that it is an antigen-antibody reaction, or that reagens or other circulating antibodies play an etiologic role. For, while various antibodies have been demonstrated in the serum of these patients, such immune substances have not been shown to mediate serum sickness. This antibody formation includes the formation of precipitins, which appear usually within a week or two after the onset of serum disease. As the precipitins make their appearance in the serum of the patient, the horse serum disappears from the patient's blood. The precipitins last *for several days to a few weeks or a month. Anaphylactic* antibodies usually accompany them. Reagins may also accompany the formation of precipitins and anaphylactic antibodies. The degree of severity of the symptoms is no index as to the *likelihood that the patient has acquired a* sensitivity to horse serum, and that future injections of horse serum may prove allergically dangerous.

Serum sickness is usually not serious, although severe manifestations may follow the use of such sera as, for exam-

ple, scarlet fever antitoxin The more severe reactions are generally ascribable to improper methods of preparation of the serum, although it is generally agreed that any pneumococcus or streptococcus serum, such as scarlet fever serum, is more likely to be followed by severe serum sickness than is caused by diphtheria antitoxin

Acquired (Accelerated) **Serum Reaction.** A patient who receives an injection of foreign serum for the second time, especially four weeks or longer following the first injection, may within a few minutes to a few hours develop a reaction. This reaction may be mild, consisting of the usual symptoms of serum disease; or it may be severe and even fatal. It differs from ordinary serum sickness in that, first, it is not preceded by the usual incubation period (3 to 14 days), and second, it occurs in patients who have previously been given serum and are now receiving it for the seond or third time Furthermore, the manifestations are more serious if the quantity of serum is greater, and if the serum be given intravenously instead of subcutaneously Acquired serum sickness may occur not only from the previous administration of therapeutic serum but also from the administration of *diphtheria* toxin-antitoxin As a matter of fact, it seems that toxin-antitoxin injections seem to favor the development of acquired serum reactions

If one injects the same serum shortly after the incubation period of serum disease is terminated, one may obtain, instead of a generalized reaction, a marked local reaction, manifested by massive swelling or inflammation and induration or even *necrosis,* without any constitutional symptoms This local reaction is similar to that described as the Arthus phenomenon in anaphylactic rabbits The mechanism of this reaction is not understood In all likelihood, accelerated serum reaction is an acquired form of allergy. It is accompanied by the presence of various antibodies such as anaphylactic antibodies, precipitins, and even

reagins. Positive skin tests are obtainable. Occasionally, although fortunately very infrequently, such an accelerated reaction may cause death. These severe reactions may occur particularly after the administration of tetanus or scarlet fever antitoxin, or the administration of horse serum for hemorrhage.

Atopic (Familial) Serum Reaction. An individual is spoken of as *atopically sensitive* if he presents a *familial* tendency to allergy, manifesting itself particularly by clinical conditions such as hay fever and bronchial asthma. The injection of even a very minute quantity of horse serum (0.1 cc) may bring about an immediate and very severe constitutional reaction in such individuals especially if they have "horse asthma," and are *sensitive to horse serum*. This type of reaction is very dangerous and is characterized by severe dyspnea, asthma, urticaria, and circulatory failure. It is controlled by employing the procedures outlined in Chapter 4.

DIAGNOSIS OF SERUM ALLERGY

History. The diagnosis of serum reactions is made by the history of previous administration of therapeutic serum such as toxin-antitoxin, and a family or personal history of hay fever or asthma, especially a personal history of "horse asthma."

Skin and Ophthalmic Tests. These should be performed before administering serum. About 0.02 cc. of horse serum diluted 1-10 is injected intradermally. It is desirable to employ for such testing not the specific immune serum but plain horse serum, because the former may yield a nonspecific, *edematous-erythematous reaction unaccompanied* by wheal formation, a reaction referred to by Foshay as the E-E reaction. In the presence of an asthmatic history, and in children regardless of the history, it is best to use a 1-100 dilution of horse serum. The appearance of a wheal

with pseudopods surrounded by an area of erythema constitutes a positive reaction. This is a simple, practical, and useful test, and *it should never be omitted* before injecting a foreign serum. Rabbit serum yields a false positive reaction in concentrations greater than 1-100, hence one always employs a dilution of 1-100 for intradermal testing with the serum.

The *ophthalmic test* is simple, safe, and fairly accurate. It consists in the instillation of horse serum into the conjunctival sac, the amount introduced being one drop of a 1-10 dilution for adults, and one drop of 1-100 dilution for children Itching of the eye and reddening of the conjunctiva indicate a positive reaction Its sphere of usefulness is limited somewhat by the fact that, if negative, it is of little significance in children

RISKS EXPECTED FROM SERUM ADMINISTRATION

The risks involved in the administration of serum may be summarized as follows the subcutaneous is always safer than the intravenous method of administration. *Purified* and concentrated products are always preferable. Serum may be given safely by any route for the *first time if there* is no personal history of allergy and *no* familial allergic history, and if both the intradermal and ophthalmic tests are negative. Serum may be given with caution, and only when absolutely necessary, to a nonallergic patient who has had serum previously, if *the* skin test to horse serum is moderately positive, or if the ophthalmic test is positive. Intravenous injections in these cases should be given in spaced injections and with *great caution* Serum may be given, but with greatest care, if the patient is allergic to horse dander, but gives a negative skin and negative ophthalmic test to horse serum The administration of serum is contraindicated when the patient is allergic (has asthma

reagins. Positive skin tests are obtainable. Occasionally, although fortunately very infrequently, such an accelerated reaction may cause death. These severe reactions may occur particularly after the administration of tetanus or scarlet fever antitoxin, or the administration of horse serum for hemorrhage.

Atopic (Familial) Serum Reaction. An individual is spoken of as atopically sensitive if he presents a familial tendency to allergy, manifesting itself particularly by clinical conditions such as hay fever and bronchial asthma The injection of even a very minute quantity of horse serum (0 1 cc) may bring about an immediate and very severe constitutional reaction in such individuals especially if they have "horse asthma," and are sensitive to horse serum. This type of reaction is very dangerous and is characterized by severe dyspnea, asthma, urticaria, and circulatory failure. It is controlled by employing the procedures outlined in Chapter 4.

DIAGNOSIS OF SERUM ALLERGY

History. The diagnosis of serum reactions is made by the history of previous administration of therapeutic serum such as toxin-antitoxin, and a family or personal history of hay fever or asthma, especially a personal history of "horse asthma"

Skin and Ophthalmic Tests. These should be performed before administering serum. About 0.02 cc of horse serum diluted 1-10 is injected intradermally. It is desirable to employ for such testing not the specific immune serum but plain horse serum, because the former may yield a nonspecific, edematous-erythematous reaction unaccompanied by wheal formation, a reaction referred to by Foshay as the E-E reaction. In the presence of an asthmatic history, and in children regardless of the history, it is best to use a 1-100 dilution of horse serum The appearance of a wheal

possible, a serum prepared from an animal other than the horse should be procured

Inasmuch as individuals develop a sensitivity to horse serum as a result of a previous injection with horse serum, and because of the increased prophylactic use of diphtheria toxin-antitoxin, the development of this type of sensitivity may be diminished greatly by encouraging the use of toxoid or goat serum toxin-antitoxin for active immunization against diphtheria, and substituting goats for horses in the preparation of the various immune sera. Allergic manifestations which at times may be severe may result from the administration of tetanus toxoid or diphtheria toxoid. They are, perhaps, a little more common from the latter. Such reactions are due to the presence of a proteose contained in the preparation, or a sensitivity to some of the culture media on which the organisms have been grown. Certainly the number of reactions is fewer than from the administration of toxin-antitoxin or other serum-containing preparations

CASE REPORT

Serum Atopy (Familial)

Case 24 Patient, male, aged 33, a physician, gave a history of seasonal ragweed hay fever and asthma extending over a period of many years. There was a strong positive family history of allergy He also gave a history of horse asthma. While waiting in a parking station to have his car delivered, he became involved in an automobile accident in which his arm was deeply lacerated and penetrated by the car door-handle. The question arose as to the advisability and safety of giving him antitetanic serum He showed a marked positive reaction on intradermal testing to 1-100 dilution of horse serum. It was therefore [illegible]
that the [illegible]

or hay fever) to horse dander, and presents a positive intradermal and ophthalmic test to horse serum (1-100). The reaction which is certain to follow under these circumstances would be so serious and the chances of controlling it successfully would be so small, that it is well to employ a therapeutic serum of a source other than horse serum if the procedure is therapeutically mandatory.

EFFICACY OF REACTION-AVOIDING PROCEDURES

In serum sickness neither the manner of injection nor the frequency and size of the dose employed can prevent the occurrence of serum sickness. This statement is modified somewhat by the fact that subcutaneous injections of concentrated serum are not so apt to produce this form of reaction; and, furthermore, that the injection of some sera (particularly streptococcus and pneumococcus sera) are more likely to be followed by serum sickness. The treatment of serum sickness includes the administration of acetylsalicylic acid, codeine, sedatives, histaminase, ephedrine, and epinephrine 1-1,000. It is also well to reassure the patient and his family of the fact that the condition is not at all serious

Acquired or accelerated serum reaction may be rendered less severe by the injection of small doses of serum with epinephrine at frequent intervals over a period of several hours

In atopic (familial) sensitivity to horse serum, desensitization is neither practical nor possible The urgency and need of serum therapy must be considered If it is a lifesaving procedure, the situation should be explained to the family, the responsibility *should be shared with another* physician, and the serum should be administered in small-spaced injections and mixed with epinephrine. If at all

possible, a serum prepared from an animal other than the horse should be procured.

Inasmuch as individuals develop a sensitivity to horse serum as a result of a previous injection with horse serum, and because of the increased prophylactic use of diphtheria toxin antitoxin, the development of this type of sensitivity may be diminished greatly by encouraging the use of toxoid or goat serum toxin-antitoxin for active immunization against diphtheria, and substituting goats for horses in the preparation of the various immune sera. Allergic manifestations which at times may be severe may result from the administration of tetanus toxoid or diphtheria toxoid. They are, perhaps, a little more common from the latter. Such reactions are due to the presence of a proteose contained in the preparation, or a sensitivity to some of the culture media on which the organisms have been grown. Certainly the number of reactions is fewer than from the administration of toxin-antitoxin or other serum-containing preparations.

CASE REPORT

Serum Atopy (Familial)

CASE 21. Patient, male, aged 33, a physician, gave a history of seasonal ragweed hay fever and asthma extending over a period of many years. There was a strong positive family history of allergy. He also gave a history of horse asthma. While waiting in a parking station to have his car delivered, he became involved in an automobile accident in which his arm was deeply lacerated and penetrated by the car door-handle. The question arose as to the advisability and safety of giving him antitetanic serum. He showed a marked positive reaction on intradermal testing to 1-100 dilution of horse serum. It was therefore apparent that the administration of horse serum tetanus antitoxin would in all likelihood be fatal. Fortunately, it was possible to locate and administer bovine antitetanic serum.

Teaching Points:

1. It is well to establish the presence or absence of an atopic personal and family history as well as the presence or absence of horse-serum sensitivity in any patient who is about to receive horse serum for therapeutic or prophylactic purposes.

2. If such sensitivity is established, it becomes necessary to procure a serum prepared from some other source.

3. Skin tests with horse serum should always precede its administration.

SUMMARY

There are three types of reactions resulting from the administration of foreign serum. These may be classified as follows: (a) Ordinary serum sickness, (b) accelerated or acquired serum reaction, and (c) atopic or familial reactions

Ordinary serum sickness results in from two to 14 days following the administration of foreign serum for the first time. It is characterized by fever, skin rash, joint pains, and edema The condition is not serious and is not accompanied by demonstrable circulating or skin-reacting antibodies

Acquired or accelerated serum reaction results from the injection of foreign serum for the second time. It comes on shortly after the injection and the reaction may be either mild or very severe and even fatal. It is in all likelihood an acquired form of allergy due to previous exposure to the same type of serum. The exact mechanism is not known It is accompanied by the presence of various antibodies including reagins. Positive skin tests are obtainable.

Atopic serum reactions occur in individuals who have a familial tendency to allergy. This manifests itself by the development of hay fever and asthma following the injection of even a minute dose of serum. The skin tests are positive. An understanding of the type of reaction which the patient develops is essential to proper management and prognosis of that condition.

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Teaching Points:

1. It is well to establish the presence or absence of an atopic personal and family history as well as the presence or absence of horse-serum sensitivity in any patient who is about to receive horse serum for therapeutic or prophylactic purposes.

2. If such sensitivity is established, it becomes necessary to procure a serum prepared from some other source.

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Atopic serum reactions occur in individuals who have a familial tendency to allergy. This manifests itself by the development of hay fever and asthma following the injection of even a minute dose of serum. The skin tests are positive. An understanding of the type of reaction which the patient develops is essential to proper management and prognosis of that condition.

11

Drug Allergy

GENERAL CONSIDERATIONS
TERMINOLOGY
DRUGS WHICH CAUSE ALLERGY
MECHANISMS AND CLINICAL MANIFESTATIONS OF DRUG ALLERGY
DIAGNOSIS
TREATMENT
CASE REPORTS
DRUG ALLERGY (DERMATITIS MEDICAMENTOSA)
ALLERGY TO ARGYROL
ACQUIRED ALLERGY TO PENICILLIN
ALLERGY TO BIOLOGIC PRODUCTS
SUMMARY

GENERAL CONSIDERATIONS

This form of allergy is caused by exposure to a drug to which an individual is sensitive. The exposure is either by inhalation, ingestion, injection, or by absorption from mucous membranes and the skin Reactions may result, therefore, from such procedures as the use of nose drops, enemas, douches, suppositories, mouth washes, and dentifrices The manifestations of drug allergy are unusual and yet characteristic The quantity of the drug producing allergic symptoms is usually very small, an amount which does not cause any manifestations in normal, nonallergic individuals

TERMINOLOGY

Drug Intolerance (Hyperergy). The toxic effect of a drug is characteristic for each individual drug The toxic effect

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MECHANISMS AND CLINICAL MANIFESTATIONS OF DRUG ALLERGY

The mechanism of drug allergy is similar to that of serum allergy. As in serum allergy it may be of several kinds.

Atopic (Familial). In the familial or atopic type, the allergy is based on the transmission by heredity of a sensitive shock organ, so that repeated exposure to the specific drug may produce an allergic reaction. This reaction is frequently immediate (asthma, hay fever) and may be very severe or even fatal. It is similar to the reaction observed in horse asthmatics who are atopically sensitive to horse serum. *The only difference* lies in the mechanism involved in the two phenomena in familial allergy to horse serum (atopy), anti-horse serum reagins are demonstrable in the patient's serum. Skin tests and passive transfer are positive The allergen is a protein. In atopic or familial drug allergy, however, no reagins against the drug are found in the blood. Skin tests and passive transfer are not positive. In other words, the patient who develops a severe attack of asthma from the ingestion of a 5-gr tablet of aspirin is atopically sensitive to aspirin, but will not show a positive skin reaction to aspirin The allergen, aspirin, *is not* a protein. It is thought that the sensitivity is a hapten-protein sensitivity, that is, a sensitivity due to a combination of aspirin with the body proteins.

Acquired There is, however, another kind of drug sensitivity which is called *acquired* drug allergy. This type resembles ordinary serum sickness. Neither reagins nor any other kind of antibodies are demonstrable in these instances, and the exact mechanism is not understood The criteria for allergic diagnosis are usually not present, except that the patient may show a blood eosinophilia

The clinical characteristics are as follows an incubation

of salicylates, for example, is different from that of digitalis. Toxic effects *are produced by greater quantities of the* drug than are used for physiologic or therapeutic purposes. Occasionally, however, an individual may show toxic effects from a relatively small dose of a drug, so that he may develop, for example, tinnitus aurium from 5 or 10 grains of salicylates. This effect is, therefore, an exaggeration of the normal action of a drug, and to this type of sensitivity the term drug intolerance or hyperergy is given. The symptoms of tolerance, like the symptoms of the toxic effects *of a drug, vary with and depend on the particular drug* involved.

Dermatitis Medicamentosa. On the other hand, an individual allergic to a drug may show a train of clinical manifestations which are dependent, not on the drug itself, but on the allergic sensitivity of the patient. These manifestations are practically always the same, regardless of the nature of the drug—i.e., whether it is aspirin, morphine, arsenic, etc. The symptoms are entirely different from those characterizing the physiologic or pharmacologic effects of the drug. A very small quantity of a drug will produce allergic manifestations. An inflammation of the skin due to drug allergy or to faulty drug elimination is also referred to as dermatitis medicamentosa.

DRUGS WHICH CAUSE ALLERGY

Following is a list of some of the drugs which may act as allergens. coal-tar and benzol derivatives, such as antipyrine, aspirin, iodoform, salol, creosote, halogens, such as bromides and iodides; opiates, belladonna, quinine, cocaine, essential oils; metals, such as mercury; strychnine, phenolphthalein, barbiturates, sulfonamides, dinitrophenol; biological products, such as insulin, liver extract, pituitrin, and *tissue extract, penicillin.*

cines; but also by various cathartic pills, headache powders, nose drops, and other medicinal agents. The diagnosis is made usually from the history.

In connection with drug allergy it should be emphasized that it may take the form of sensitivity to an ointment which is applied for an allergic dermatitis. For this reason patch tests should be performed with all such suspected preparations. Also, an allergic patient may acquire an allergy to a drug used for topical application in the nose The author has recently described a case of acquired allergy to argyrol which was used for local nasal treatment. There have been many reports of acquired allergy to sulfa drugs used as ointments for local application in certain skin infections or to the drug taken by mouth. In view of the marked disturbance brought about as a result of sensitivity to sulfonamides, and in view of the widespread usage of these drugs, it is important to bear in mind the possibility of such allergy

Specific Diagnosis. Specific points on the basis of which the diagnosis of drug allergy is made are as follows

1 The presence of an incubation period The patient has been receiving some medication for a time prior to the development of his manifestations The exposure may be by injection, inhalation, ingestion, or topical application

2 *Drug allergy should* be suspected in any dermatoses of doubtful etiology. The skin lesions of drug allergy may mimic every known dermatologic condition

3 The character of the skin lesions may be suggestive of drug allergy.

4 The dermatitis may be reproduced by readministration of the suspected drug

TREATMENT

Avoidance is the chief principle in the treatment of drug allergies It involves early recognition of the fact that the

period intervenes between the administration of the drug and the appearance of the symptoms. This period varies from a few hours to a day. Fever frequently occurs, and may be produced even by the administration of antipyretic drugs, such as quinine and antipyrine. Multiform skin eruptions may occur. Urticaria is probably the most common form of skin rash and is seen following aspirin therapy.

However, other forms of dermatitis are frequently seen: eczema may develop following the administration of ephedrine and procaine; purpura from arsphenamine, iodides, and sulfonamides; lesions which are acneform from bromides and iodides; erythema nodosum from iodides and bromides, erythema multiforme from phenolphthalein and antipyrine; fixed and circumscribed skin eruptions (erythematous, bullous, or pigmented) are brought about by phenolphthalein and antipyrine, and occasionally by arsphenamine. Accompanying these skin lesions there is usually more or less severe pruritus.

The exact method of production of the dermatitis or the reason for the morphologic difference of the lesions is not known The dermatitis from sulfonamides, however, is thought to be due at least in some instances to photosensitization of the skin Occasionally, these patients may have some swelling of the joints and of the lymph nodes. Granulocytopenia results from allergy to certain drugs, such as amidopyrine and dinitrophenol, both of these drugs may be found in proprietary preparations and, therefore, may not be easily recognized Involvement of any of the viscera may take place. This type of reaction may therefore be slight or very severe and in some cases fatal.

DIAGNOSIS

General Factors. One must always keep in mind the possibility of drug allergy when treating an allergic patient Drug allergy may be produced not only by prescribed medi-

scaling erythema of a bright red color, occurring in large patches and sheets on the trunk, and of a dull red color on the face, neck, and extremities The brighter red areas were slightly puffy and all areas were intensely itchy. No adenopathy or fever was present. The arms and upper back showed some parallel bleeding excoriations, made by the fingernails.

Subsequent questioning elicited the information that the patient had suffered from insomnia for years, and that he would take chloral hydrate during periods when he was under severe nervous strain and his sleeplessness was worse At such times the dermatitis would reappear or become worse On several occasions when he applied an ointment to the skin, his condition became worse.

Teaching Points·

1 It is important to find out from a patient who is suffering from a dermatitis the nature of which is not clear, whether he is taking any drugs

2 The etiologic diagnosis of drug allergy cannot be established by intradermal or scratch tests

3. An existing dermatologic lesion may be made worse by the local application of a drug to which the patient is sensitive. Patch tests establish the presence of contact dermatitis of this type.

Allergy to Argyrol

CASE 26 Patient, male, aged 26, had had seasonal hay fever for four years. Asthmatic breathing first developed at the end of the 1941 hay-fever season. It further appeared that the ingestion of even a very small quantity of milk gave rise to violent cramps and diarrhea. He presented evidence of considerable *infection* in *the* paranasal sinuses. Considerable sneezing, nasal blockage, rhinorrhea, and even wheezing would develop during the course of local treatments with the drug, on one occasion necessitating the administration of epinephrine. Some time later severe asthma followed spraying of the throat with argyrol for pharyngitis It finally became obvious that the patient's discomfort was

patient's urticaria is brought about or is made worse by the very sedative which he is receiving to relieve him. For this reason, every allergic patient should be specifically instructed not to take drugs unless he is directed to do so by his physician. Palliative treatment includes the administration of sedatives, epinephrine, ephedrine, local applications, catharsis, and diuresis. Results from desensitization



FIG. 34. Dermatitis medicamentosa (chloral hydrate).

have been unsatisfactory. Vitamins C and K may be of value in purpura. Hospitalization may be necessary in some instances. Where the administration of a drug is essential to life, as in the administration of sulfa drugs, it may be possible to change from one drug to another in the same group

CASE REPORTS

Drug Allergy (Dermatitis Medicamentosa)

CASE 25. (See Fig 34) Patient, a middle-aged white male, gave a history of having had a skin rash at various intervals since 1933. This condition at times became very troublesome, and was accompanied by severe itching. At the time of the examination, the patient presented a diffuse non-

to the protein vehicle of argyrol or to the combination of argyrol with this protein vehicle. In contrast to the type of allergy to acetylsalicylic acid, positive reactions were obtained in this case to colloidal protein solutions of the drug

2. One wonders whether the supposed rarity of the occurrence of allergy to argyrol in nose and throat practice may not be due to a failure to recognize its presence. Patients receiving such treatments frequently protest about the discomfort it causes them, and in many instances it is not easy to recognize this discomfort as an allergic manifestation because the primary symptoms from which the patient seeks relief are so similar to those which develop coincident to treatment In other instances the reaction may be too mild to be recognized It is therefore thought likely that rhinologists who suspect a possible allergic reaction following the use of argyrol may do well to change to some other mild protein silver preparation and avoid these allergic reactions without depriving the patient of the desired therapeutic effect

3 It is generally agreed that the therapeutic effect of all mild protein silver preparations is about the same. In view of this, it may be advisable to change from one preparation to another at stated intervals in the treatment of patients who receive regularly local applications of such preparations and thus avoid the development of allergic manifestations

Acquired Allergy to Penicillin

CASE 27 Patient
history
with his
agnosed
He received massive daily doses of penicillin a year ago for a period of about three or four weeks. At the end of this period the drug had to be discontinued because the patient developed severe generalized massive urticaria with each injection Since the injections were given three or four times a day,

more than that usually experienced from the mechanical irritation of the nasal tampons, hence local treatments with argyrol were discontinued.

Scratch (skin) tests performed with a weak (1 per cent) solution of argyrol produced a definite local reaction while a control test with the drug on another person was negative. Similarly, an intradermal test with a 1 per cent argyrol solution yielded a very severe local and a mild constitutional reaction. The ophthalmic test was positive with argyrol. Controls were uniformly negative.

As an aid in determining the specificity of these reactions, passive transfer tests were done. One-tenth cc. of the patient's serum was injected intradermally into the arm of a normal person and 24 hours later 0.05 cc. of 1 per cent solution of argyrol was injected into the sensitized site. A definite local reaction resulted, indicating the presence in the patient's serum of specific antibodies (reagins) against argyrol. Controls were negative. It would therefore appear that the patient is specifically sensitive to argyrol—first because of the presence of demonstrable antibodies (reagins) in his serum and second because of the development of a *constitutional reaction on exposure.*

Teaching Points:

1. This instance of allergy to argyrol is of interest because, unlike most instances of drug allergy, it is associated *with demonstrable specific antibodies.* There are persons who, as a result of sensitivity to drugs such as acetylsalicylic acid, may have a severe and even a fatal attack of asthma following the ingestion of even small doses of the drug. However, because of the nonprotein nature of the drug, specific antibodies are not demonstrable in the serum of such patients. Skin testing to acetylsalicylic acid and similar drugs is usually not of any value. It is thought that in these instances the allergy is to a combined protein, a combination of the drug *with protein body molecules.* This patient did not have any cutaneous reactions to solutions of silver nitrate. It is obvious, then, that the allergy must be either

11 and 13 and December 21. These injections were discontinued for about one month and resumed on February 5 of the following year, without any reaction. On February 16, after receiving 3 cc of tissue extract, the patient developed an immediate reaction consisting chiefly of generalized urticaria which responded to the subcutaneous administration of epinephrine hydrochloride 1:1,000. At that time he showed 2 per cent blood eosinophilia. The next dose was given on February 21 and twice a week until March 20, without any reaction. The injections were resumed on April 23, without any untoward reactions.

Teaching Points.

1 It is obvious from what precedes that the type of reaction developed by these two patients (Cases 28 and 29) is a form of acquired or induced allergy to tissue extract. This reaction bears the characteristics of acquired serum reaction.

2 Both patients took the injections of tissue extract at first without showing any untoward reaction. In other words, previous exposure or contact was necessary to produce the allergy. The reaction in one patient (Case 28) was, in the opinion of the authors, definitely of the atopic type; namely, asthma and urticaria. This patient gave a previous history of attacks of coughing, and, while the hereditary factor is not clearly evident, there are reasons to consider him atopic. The reaction in the second patient (Case 29) was clearly more of the clinical reaction observed in acquired serum allergy.

3 A study of many of the reported instances of allergy to biologic products reveals a very interesting observation. Many of the patients had been receiving insulin, liver, pituitary, and (in both Case 28 and Case 29) tissue extract over a fairly long period of time at regular intervals without any allergic manifestations. The allergic reaction usually developed after the second or third injection following a lapse of time during which the patient did not re-

24 hours. At the time of this reaction the patient showed an eosinophilia of 7 per cent.

In view of the seriousness of the reaction and in order to study the possible mechanism which produced it, treatments were discontinued for about one month. On February 5 of the following year, however, he was given another injection of 3 cc. of tissue extract, without developing any reaction Five days later, upon receiving the next dose of tissue extract, the patient developed another general reaction, similar to, but less severe than, the first. Treatments were resumed on February 20 and continued in doses of 3 to 4 cc. at weekly intervals for three weeks, then every second day until March 20 (a total of nine injections) without any untoward symptoms. On April 23 the patient was given an injection of 4 cc of tissue extract, and the treatments were continued every five days without any reaction.

Case 29. Patient, male, aged 41, was admitted to the hospital in November, complaining of cramplike pains in the calves of both legs, especially noticeable on walking. This condition had been present for several years, becoming progressively worse, so that at the time of admission the limit of his walking tolerance was about half a city block His feet were very cold in the winter. Within the past year, he had experienced numbness of the fingers of the right hand and pain under the nails When immersed in cold water, the fingers became very painful He smoked to excess. There was no history of asthma, hay fever, eczema, or allergy to drugs. There was no family history of allergy

The general physical examination was negative, and examination of the upper extremities was negative. There were no demonstrable trophic changes in the nails of the toes. On dependence the toes assumed a reddish hue which quickly faded on elevation, leaving a cadaveric pallor. Samuel's test was negative. Dorsalis pedis, posterior tibial, and popliteal vessels were not palpable Femoral pulsations were apparently normal. Oscillometric readings were zero in both the right and left foot and ankle and were reduced in both calves.

General treatment for thrombo-angiitis obliterans of both legs was instituted. The patient received 3 cc. of deinsulinized pancreatic tissue extract intramuscularly on November

6. The evidence points to the presence in these instances of a sensitivity to pancreatic tissue protein and not to the muscle protein of the animal from which the pancreas was obtained In other words, we are dealing with an organ and not a biologic source sensitivity This evidence is based largely on two considerations: first, the presence of reagins in the serum of Cases 28 and 29 sensitive to the proteins of the pancreas regardless of whether it was hog or beef pancreas and the absence of reagins to the muscle protein of these animals, and, second, on clinical grounds, the demonstration that such patients will continue to show clinical sensitivity when given pancreatic tissue extract regardless of its source, i.e., the mere changing of the batch of the extract will usually not render its administration harmless One should point out the possibility that tissue extract or pancreatic extract may contain a very small amount of the serum of the animal from which it is obtained and that the small quantity of serum may play a role in the immunologic studies carried out in this investigation May it be that the reason some insulin-sensitive patients are found occasionally to tolerate insulin of a different source is because the patient frequently loses his insulin sensitivity spontaneously? There is no prediction when an allergic reaction to a biologic product may develop or when it will fail to develop A patient may show a reaction to an injection today, none for the next two or three injections, and then another reaction later. These patients do not react with the same unfailing constancy following exposure to the respective allergens that atopic persons, such as hay fever patients, show when exposed to pollen.

7 Similarly, spontaneous loss of sensitivity may explain the reports of successful, complete desensitization which occasionally appear in the literature. The authors tried this method of desensitization in a previously reported instance

ceive any treatment. This observation is of some interest because it reminds one of the presence of an incubation period in anaphylaxis preceding the effective shock dose

4. Attempts at experimental production of allergy to biologic products by repeated administration over a period of time have been no more successful than similar attempts at inducing at will many other forms of allergies in the human being. Obviously, only a small percentage of the large number of patients receiving biologic products such as insulin, tissue extract, etc., develop an allergy to them Indeed, these instances are so rare that, when they occur, it is considered worth while to report them It seems, therefore, that exposure alone is not sufficient to bring about the development of an acquired sensitivity of this type. Nor is the presence of an hereditary or atopic shock tissue, such as is found in atopic persons, a factor, for we have been just as unsuccessful in sensitizing atopic persons as others to biologic products.

5. What is the role of specific skin-sensitizing antibodies or reagins in acquired allergy to biologic products? Both Case 28 and Case 29 showed definite specific skin-sensitizing antibodies or reagins at the time of their reaction Both patients, however, continued to show these reagins in the same concentration for months following their reaction and at periods when they received by injection numerous doses of tissue extract without any untoward manifestations. Apparently the quantity of reagins present had little to do with the severity of the allergic reaction, for Case 28, who manifested the severest reaction, showed by passive transfer tests a comparatively smaller quantity of tissue extract reagins than Case 29, who had a milder general reaction. These reagins are incidental immune bodies in acquired allergy and play no role in the acquired allergic reaction. They differ from atopic reagins in that they are less permanent and are found in smaller concentration

sults. Intramuscular injections were therefore discontinued, and autolyzed liver concentrate (from another supply source) by mouth was substituted. The patient showed no ill effects from this preparation, which he took for about six months At this time (October) it was discovered that he could again tolerate two different makes of liver extract by injection.

Physical examination was negative except for the presence of an enlarged spleen Laboratory tests were negative except for the typical blood picture and reticulocyte response characteristic of pernicious anemia. Intradermal tests showed positive reactions to ragweed pollen and to several other allergens

Teaching Points:

1 The sensitivity demonstrated by this patient is an acquired allergy and is analogous to that of insulin and to solutions of posterior pituitary

2 The sensitivity is to an organ and not to a biologic source.

3 Positive skin tests and reagins are present for at least three months following the initial reaction.

4 Loss of clinical sensitivity is coincident with the disappearance of reagins Precipitins are demonstrable at the same time as reagins No anaphylactic antibodies are demonstrable in the patient's serum This type of acquired allergy cannot be produced experimentally.

SUMMARY

Drug allergy results from exposure to a drug Exposure may take place by inhalation, ingestion, injection, or absorption from the mucous membrane and skin. One must differentiate between drug intolerance or hyperergy, and drug allergy Almost any drug may act as an allergen, but some are more frequent offenders than others. The mechanism of drug allergy is in many respects similar to that of serum allergy. There is a familial and an acquired type of

of liver extract allergy and failed. Had *so-called desensitization* been attempted in Case 28 by repeated administration of small doses of tissue extract shortly after he developed the allergic reaction, his subsequent tolerance of tissue extract naturally would have been interpreted as being caused by this procedure and not by a spontaneous loss of sensitivity as the facts indicate. However, it may be possible that extensive treatment with a given extract may exhaust the majority of circulating antibodies or in some other manner lead to a state of hyposensitization. It must be pointed out that there *is no evidence that there was any diminution in* the amount of demonstrable reagins in Cases 28 and 29 as a result of continuous treatment with tissue extract. As a matter of fact, there is evidence that there was an actual increase in these reagins at first, a finding analogous to that obtained in the treatment of hay fever.

Allergy to Liver Extract.

CASE 30. Patient, male, white, aged 41, had a long-standing history of anemia and ragweed hay fever as well as a history of clinical sensitivity to various foods The ingestion of strawberries gave him urticaria He got severe gastro-intestinal upsets with nausea, vomiting, and abdominal pain from eating the skin of apples, the bulk of oranges, and cabbage. He presented no family history of allergy.

A diagnosis of pernicious anemia was made, and liver therapy by injection was instituted in February. The patient received liver extract intramuscularly at intervals of ten days for a period of one year without showing any untoward reaction Clinical improvement was marked Treatment was discontinued during April of the following year, but resumed during the first week in May. Shortly after the third injection in May, a marked reaction developed consisting of severe asthma and generalized urticaria. *This* reaction lasted for from seven to 12 hours In order to make certain that the reaction was due to the administration of liver, it was repeated the following week, with identical re-

BACTERIAL SENSITIZATION

In other instances, however, exposing the body to certain bacteria brings about the development not of protection but of an allergy either to the bacterial body protein itself or to the bacterial secretion. This is not a form of antibacterial immunity but a state of lack of protection against the bacteria or their products This type of reaction is referred to as hypersensitiveness of infection or bacterial allergy which is thought by many to be actually a phase in the development of immunity to infection. Bacterial allergy may manifest itself in the form of anaphylaxis (in lower animals) or in various forms of clinical allergy.

The bacterial body or occasionally its secretory product must have two types of allergens One type or fraction is in every way similar to that of nonbacterial protein and can actively sensitize lower animals, giving rise to bacterial anaphylaxis For example, it is possible to sensitize guinea pigs anaphylactically by the injection of *tuberculin*. Another constituent of bacterial body may give rise to manifestations of allergy such as bronchial asthma. Still another constituent of the bacteria is the carbohydrate fraction which, when introduced into an animal, may unite with the tissue proteins, giving rise to a hapten. In this case the allergy assumes the form of the delayed tuberculin type of reaction This fraction by itself cannot act as an allergen to evoke an allergic reaction

BACTERIAL ALLERGY IN ASTHMA

There is little doubt as to the probability of the existence of a state of allergy to the proteins of bacteria, especially when the infection is in the respiratory tract. This type of sensitivity is acquired, but may be found in atopic as well as nonatopic individuals It accounts, in all likeli-

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Bacterial Allergy

ANTIBACTERIAL IMMUNITY RESULTING IN PROTECTION
BACTERIAL SENSITIZATION
BACTERIAL ALLERGY IN ASTHMA
BACTERIAL ALLERGY AND ACUTE INFECTIONS
TUBERCULIN TYPE OF ALLERGY
THE SHWARTZMAN PHENOMENON
ACQUIRED FUNGUS ALLERGY
CASE REPORT
SUMMARY

ANTIBACTERIAL IMMUNITY RESULTING IN PROTECTION

The subject of bacterial allergy is of importance in connection with the study of infection and immunity. Upon being injected with certain bacteria or their secretions or toxins, an animal will frequently produce antibacterial or antitoxic immune substances. These will destroy the bacteria or their secretions and thus protect the tissues. Thus, a toxin-producing bacterium, the diphtheria bacillus, stimulates the formation of a protective substance, antitoxin, which is demonstrable by the Schick test. Bacteria such as the tubercle bacillus, the typhoid-colon group, and others stimulate the production of antibacterial antibodies which are demonstrable by the agglutination and complement-fixation tests. This is a type of antibacterial immunity which results in protection and may last for a variable period of time.

BACTERIAL SENSITIZATION

In other instances, however, exposing the body to certain bacteria brings about the development not of protection but of an allergy either to the bacterial body protein itself or to the bacterial secretion. This is not a form of antibacterial immunity but a state of lack of protection against the bacteria or their products. This type of reaction is referred to as hypersensitiveness of infection or bacterial allergy which is thought by many to be actually a phase in the development of immunity to infection. Bacterial allergy may manifest itself in the form of anaphylaxis (in lower animals) or in various forms of clinical allergy

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BACTERIAL ALLERGY IN ASTHMA

There is little doubt as to the probability of the existence of a state of allergy to the proteins of bacteria, especially when the infection is in the respiratory tract. This type of sensitivity is acquired, but may be found in atopic as well as nonatopic individuals. It accounts, in all likeli-

hood, for the close etiologic relation between infection in the nose and bronchi, and the development of asthmatic symptoms. The immunologic basis for this form of allergy is not altogether clear. The presence of reagins against bacterial proteins has not been conclusively proved. Passive transfer is not easily demonstrated. Occasionally a patient may develop a constitutional reaction as a result of receiving an injection of vaccine, but such reactions cannot be produced at will, nor are they as frequent as constitutional reactions resulting from the administration of pollen extracts in hay-fever patients. For these reasons, positive skin reactions obtained from skin testing of asthmatic patients with bacterial suspensions must be accepted with skepticism. Nevertheless, patients suffering with asthmatic bronchitis are benefited by treatment with properly prepared sputum vaccines.

BACTERIAL ALLERGY AND ACUTE INFECTIONS

Rheumatic Fever. Some workers are of the opinion that rheumatic fever may be a form of sensitization of the joint membranes to the streptococcus. Streptococci are found *practically* always associated with rheumatic infections and are usually present in a focus. Specific antibodies such as precipitins, agglutinins, and complement-fixing antibodies are frequently demonstrable in these instances. It is thought that the organism found in the focus secretes products which are carried by the blood to the sensitized tissue of the joints. The joint lesions are, according to this view, in reality allergic phenomena. In the same sense it is considered that previous infection with the rheumatic fever agent sensitizes the heart valves to subsequent involvement of subacute bacterial endocarditis by the *Streptococcus viridans*. There is a great deal of evidence which points to the plausibility of this theory.

Scarlet Fever. A similar relation may occur in connection with scarlet fever. It is claimed by some that part of the symptoms of scarlet fever, the rash, vomiting, arthritis, and hematuria, are due to an allergy to a soluble exotoxin. The theory is that as the infant develops successive streptococcal infections he becomes allergic, so that subsequent massive infection with the same organism gives rise to a generalized allergic reaction which manifests itself as the toxic symptoms of scarlet fever. This would explain the occurrence of Dick-negative reactions in a large number of adults who have never had scarlet fever.

TUBERCULIN TYPE OF ALLERGY

Probably still another type of bacterial allergy is that to the secretory products of bacteria For, long after the active infection with such organisms as the tubercle bacillus has disappeared, the individual will show evidence of sensitivity to the secretion of the tubercle bacillus; namely, to tuberculin This sensitivity is readily demonstrable by the development of a local reaction 24 hours after an intradermal injection with tuberculin If the tuberculin is injected intravenously, a constitutional reaction may develop. At any rate, the reaction may be local, focal, or constitutional, depending on the dose and route of administration. This type of tuberculin reaction is similar to that of the mallein reaction in glanders, trichophyton reaction in trichophytosis, and abortin reaction in abortus infection and the Frei test in granuloma inguinale, all of which are described in Chapter 17

Mechanism. The exact mechanism of the tuberculin type of skin reaction is not understood The antibodies involved have not as yet been satisfactorily demonstrated. Previous infection with the organism is a prerequisite to a subsequent positive reaction. However, previous injection with tuberculin will not produce tuberculin allergy. Infection,

and infection alone, with the tubercle bacillus, and the subsequent development of a tubercle are essential to the development of a delayed tuberculin reaction. Hence, the *property of the infected tissue* must play an all-important part in the production of this type of allergy.

Manifestations. Exception is taken to these conclusions by those (Seibert, Eberson, Zinsser) who have shown that a skin sensitivity to tuberculin may be produced experimentally in normal nontuberculous guinea pigs and rabbits by injecting these animals first with highly purified, undenatured protein of tuberculin. A sensitized animal will develop *a local reaction at the point of subsequent injection* of tuberculin. This reaction consists of an area of inflammation, induration, necrosis, etc. The failure of previous workers to produce active sensitivity is said to be due to the fact that they have used TO, a poor antigen for this purpose.

THE SHWARTZMAN PHENOMENON

This is not an anaphylactic phenomenon, but it bears sufficient resemblance to the tuberculin type of allergy to be discussed here. It is essentially a form of skin sensitivity to bacterial culture filtrates. Shwartzman has shown that if a small amount of culture filtrate of *B typhosus* (*Eberthella typhosa*) is injected intradermally into a rabbit, no reaction occurs. However, if one reinjects this animal intravenously 24 hours later with the same culture filtrate, there will appear at the point of previous subcutaneous injection a hemorrhagic area. If the intravenous injection is made 48 hours later, no reaction occurs Obviously, the first injection *sensitized* or *prepared* the skin for the reaction. This is probably a manifestation of local tissue allergy. It is interesting that this reaction cannot be produced by the

injection of other proteins such as egg albumen or horse serum Shwartzman states that not even all bacterial filtrates can produce it.

ACQUIRED FUNGUS ALLERGY

The dermophytid type of skin involvement referred to in Chapter 9 is a form of acquired allergy to fungi In these instances one obtains a positive delayed tuberculin-like reaction to an extract of fungi This reaction is described in detail in Chapter 13.

CASE REPORT

CASE 31 Patient, aged 52, complained of severe paroxysms of asthmatic breath [illegible]
years [illegible]
respira[illegible]
night [illegible] with a severe, very productive cough. There was no family history of allergy There was no personal history of associated allergic manifestations The intradermal tests were negative The blood count showed a moderate leukocytosis, but no eosinophilia. Examination of the nose presented evidence of chronic suppurative sinusitis for which the patient was operated on and treated subsequently.

This patient received the usual treatment consisting in the administration of *iodides*, ephedrine, epinephrine, etc. Administration of respiratory vaccine in a dose of 0 1 cc. was followed on more than one occasion by a severe constitutional reaction. As a result of this, the vaccine was diluted 1-10 Passive transfer tests with this vaccine are negative Bronchoscopic treatment gave the patient symptomatic relief

Teaching Points

1 This is an instance of severe, intractable bronchial asthma resulting from an acquired allergy to infection (bacteria in the upper respiratory tract)

13
Fungus Allergy

FREQUENCY
DISTRIBUTION OF SPORES OF FUNGI
LABORATORY CONSIDERATIONS
ATOPIC SENSITIVITY TO FUNGI
ACQUIRED FUNGUS ALLERGY (DERMOPHYTID)
SKIN TESTING WITH MOLD EXTRACTS
TREATMENT
CASE REPORT
SUMMARY

FREQUENCY

It is only in the last few years that we have come to realize the importance of fungi in clinical allergy. The great difficulty in connection with this subject is the fact that recognition and isolation are not easy because of the great number of different species of fungi. Their wide distribution and the ease with which fungi grow also add a laboratory problem; namely, that of contamination. Despite these difficulties, allergists have come to realize the importance of fungi in allergy, and include them among the standard allergens used in testing.

About 10 per cent of allergic patients give positive reactions to molds. Molds occur both outdoors and indoors. Some are more important as inhalant allergens than others The commoner and more important ones which should be included in diagnostic testing are. Alternaria, Hormodendron (Cladosporium); helminthosporium, Aspergillus flavus, fumigatus, nidulans, niger, and oryzae, Penicillium digitatum and glaucum; Rhizopus necans; Chaetomium; monilia sitophilia; Mucor plumbeus, trichoderma, grain

smut; Trichophyton; Saccharomyces (bakers' and brewers' yeast) and others These fungi grow abundantly, and are found in damp, mildewed places Sensitive individuals frequently complain of sneezing or asthma when exposed to the spores, as when they go to the cellar or basement Others develop symptoms for several weeks after they move to a summer cottage which has been closed for the winter.

DISTRIBUTION OF SPORES OF FUNGI

Some fungi such as Alternaria, Hormodendron, Penicillium, Aspergillus, Mucor, and a few others have a definite seasonal distribution varying in abundance with the part of the country, its proximity to the wheat belt, and various climatic conditions, such as rain, wind, sunshine, and temperature The season for Hormodendron and Alternaria, for example, lasts from May to September in the Pittsburgh and Chicago district, and the spore content of the air is about the same throughout this interval This would indicate that patients who have hay fever or asthma during these months and give negative pollen reactions might well be sensitive to fungi Especially is this true if the patient's condition should continue during the month of July, when there is usually a let-up in hay-fever symptoms. It was observed that the distribution of Alternaria follows somewhat the prevalence of ragweed pollen and geographically the wheat- or grain-growing belt

Yeasts are food allergens, being contained in bread, beer, and cakes Hormodendron (Cladosporium) is found as frequently as Alternaria

The dermatophytes are a group of molds which infect the skin and its appendages The group includes Microsporon and Trichophyton, which produce ringworm of the skin, Epidermophyton, which involves the web of the fingers, the axilla, and the groin, and Microsporon, which produces pityriasis versicolor. The common infection of the

type of delayed intradermal reaction, or one may occasionally demonstrate a positive patch test with Trichophyton. This noninfectious but allergic dermatitis is referred to as dermophytid.

SKIN TESTING WITH MOLD EXTRACTS

For the purpose of skin testing for acquired allergy to fungi, Trichophyton extract is employed in a dilution of *1-30, and oidiomycin in a dilution of 1-100. 0.1 cc. is in*jected subcutaneously for the delayed test. The patient may also present *a positive patch test to these extracts, indicat*ing a contact type of dermatitis. The regular intradermal test with extract of fungi is employed, however, in patients suspected of atopic (familial) sensitivity.

TREATMENT

It is not always easy for a patient with inhalant fungus allergy to avoid exposure to fungi Air filtration will help to reduce the spores, but they are so widely distributed in the furniture, carpets, pillows, and other articles that avoidance *is quite difficult.* Frequently, *for example, what seems* to be an allergy to a feather pillow is in reality an allergy to the molds growing in a feather pillow. Patients sneeze and cough when exposed to an old feather or kapok pillow, but are unaffected by exposure to a new, mold-free pillow.

Desensitization or, more properly, hyposensitization is frequently the procedure of choice in the treatment of individuals atopically sensitive to fungus spores. The patient is given, subcutaneously, increasing doses of an extract of the fungus to which he is sensitive, beginning with 0.1 cc. of a 1-1,000 *or 1-100 dilution, and increasing by 0.1 cc.* every week until 1 cc. dose is reached At this time the concentration of the extract is increased and he receives 0 1 cc. of a 1-100 or 1-10 dilution, and the dose is stepped up until he is given 0.1 cc. of a 1-10 or of a concentrated extract. In

he case of Trichophyton, one begins with 0.1 cc. of a 1-100 dilution or a weaker dilution if necessary; in the case of oidiomycin one begins with the injection of 0 1 cc. of a 1-200 or 1-300 dilution The dose is increased depending on the local reaction Occasionally, hyposensitization with extracts of the offending fungi is employed in the treatment of acquired fungus allergy as in dermophytids, although the therapeutic results thus obtained are not so good as they are in other types of fungus allergy.

CASE REPORT

For a case report of allergy to spores of fungi, see Case 40, p 332

SUMMARY

Fungus allergy may be either acquired or atopic. The acquired form is similar to tuberculin sensitivity and plays an important role in the development of certain forms of allergic dermatoses referred to as *dermophytids*. *In these* instances the allergy is due to the secretory products of a fungus with which the patient was initially infected. Fungus allergy is also of some etiologic importance in atopic patients where the allergy is due to the *protein of fungus* spores In these instances the manifestations involve the respiratory tract and are present at the time of the year when the spores are found in the air.

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Physical Allergy

ALLERGY TO HEAT, COLD, SUNLIGHT, AND EFFORT
DIAGNOSIS
TREATMENT
CASE REPORTS
ALLERGY TO COLD
ALLERGY TO SUNLIGHT
SUMMARY

ALLERGY TO HEAT, COLD, SUNLIGHT, AND EFFORT

Physical allergy includes sensitivity to heat, cold, effort, and sunlight Medical literature contains an abundance of case reports illustrating this form of allergy, so that these instances are no longer considered rarities.

DIAGNOSIS

The diagnosis of physical allergy is not always easy, because the condition is frequently complicated. Exposure to cold, for example, may elicit symptoms in the summer but not in the winter Some patients will show allergic manifestations to heat only when breathing cold air. Sensitivity to sunlight may result in a severe dermatitis at the point of exposure to the least amount of sun rays The specific diagnosis of physical allergy is made by proper exposure to effort, to heat, to cold, or to sunlight The history, however, is diagnostic in many instances. Thus, a young girl complains of attacks of massive swelling of the face when going in swimming Another patient complains of attacks of asthma when exposed to cold weather

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nent involves the use of a powder, lotion, or salve to protect the skin from the light rays, but this procedure is not always practical. In some cases correction of gastro-intestinal pathology and the administration of vitamins C and B_2, and a diet free of animal proteins, have proved valuable.

CASE REPORTS

Allergy to Cold

CASE 32 Patient, male, aged 46 (see Figs. 35 and 36) stated he had been troubled with attacks of localized massive swellings for the past six years. These occurred



FIG 35 Allergy to cold. Note swollen right hand as compared with left hand following immersion of right hand in cold water.

wherever and whenever cold struck his skin. A cold wind, walking on snow, sitting on a cold stone, produced large swelling of the involved parts Immersion of one hand in ice water caused his hand to become swollen to twice the normal size. At the same time, his face became flushed and he became dizzy, indicating a possible histamine or reflex effect This condition was relieved by activity, effort, and by heat.

The mechanism of physical allergy is not clear. In most instances, it is supposed that the symptoms result from the liberation of a histamine-like substance. In the case of sun sensitivity, the reaction may be truly allergic, or it may be due to the presence in the skin of a photosensitizing medium which, upon proper exposure to certain rays of the spectrum, will give rise to a dermatitis. This sensitizing agent may be produced within the body from the blood, as in the presence of bleeding peptic ulcers, from animal protein within the intestinal tract, or as a result of the ingestion of certain substances such as drugs (sulfonamides, barbiturates, etc.). The dermatitis may assume various forms. It may be either an acute or subacute dermatitis. It may result from exposure to the ultraviolet portion or to the yellow or red portion of the spectrum.

TREATMENT

Treatment consists in avoidance of the exciting factors when possible. "Desensitization" has been undertaken with some measure of success. This consists in exposing the patient very gradually to increasing doses of cold or heat, as the case may be, by suitably adjusted bath temperatures Thus, in a heat-sensitive patient, the individual is exposed to a heat lamp which is barely warm, and the intensity of the heat is gradually increased. The patient is intermittently exposed, following each treatment with heat, to some degree of cold, for it has been found that this alternating procedure is therapeutically effective. Combined with this treatment, belladonna by mouth and histamine injections are given, according to the schedule described in a previous chapter. In some instances relief has been obtained by treatment with histaminase.

The treatment of sunlight dermatitis has not been too successful. Exposure to gradually increasing doses of ultraviolet rays has not been always effective. Preventive treat-

Allergy to Sunlight

CASE 33. Patient, female, aged 48, stated that she had been troubled with a sunlight allergy and dermatitis as [illegible] came quite serious and very disturbing The patient found that she could never go out in the daytime. The only time [illegible] here [illegible] re a [illegible] der-matitis There was no hay fever or asthma. [illegible] had asthma Her brother and sister had had asthma. There was no allergy to foods, but she had an allergy to drugs, as, for example, bichloride of mercury in any form, aspirin, and luminal, from the latter of which she got a dermatitis of the mouth and lips. Sunlight even coming through glass produced a dermatitis For this reason she sought employment in Pittsburgh, where she was told there is hardly any sunlight. However, she found that her condition still bothered her considerably after her arrival there.

Teaching Points:

1. Strong family history of allergy in this case.
2. Association with poison-ivy dermatitis.
3. Association with drug allergy.
4. Some cases of sunlight allergy are truly allergic and passive transfer is demonstrable
5. Diagnostic procedures involve the mask method, in which the patient wears a mask during the daytime, or the dark-room test

SUMMARY

Physical allergy includes sensitivity to heat, cold, effort, and sunlight. The manifestations may be those of urticaria and angioneurotic edema or asthma. The diagnosis is made from the history and trial exposure. Treatment includes

Teaching Points:

1. This is an instance of allergy to cold. Exposure in these patients is thought to release histamine or a histamine-like substance which affects the permeability of the capillaries.

2. While angioneurotic edema due to cold is ordinarily not dangerous, it may easily prove to be if it occurs in the glottis. Occasionally, death of good swimmers may be due to cold allergy producing sudden massive angioneurotic edema of the glottis, resulting in asphyxia. There is usually no postmortem evidence of water in the lungs in these instances.



FIG. 36. Allergy to cold. Note large wheal on back following rubbing skin with ice (same patient as Fig. 35).

3. The clinical condition may be reproduced by exposure to cold, such as the rubbing of a piece of ice on the back or immersion of the hand in cold water. Following this procedure there develops an area of localized edema and reflex flushing of the face.

Allergy to Sunlight

CASE 33. Patient, female, aged 48, stated that she had been troubled with a sunlight allergy and dermatitis as long as she could remember. Whenever she was exposed to the sun, she broke out and became very itchy. Other parts [illegible] ed. Her condition at times be- [illegible] The patient found [illegible] ime. The only time she went out was when she could get transportation where she was shielded from the sun's rays She usually wore a large hat, and used a parasol. She also had a primrose dermatitis. There was no hay fever or asthma Her mother had asthma. Her brother and sister had had asthma. There was no allergy to foods, but she had an allergy to drugs, as, for example, bichloride of mercury in any form, aspirin, and luminal, from the latter of which she got a dermatitis of the mouth and lips. Sunlight even coming through glass produced a dermatitis For this reason she sought employment in Pittsburgh, where she was told there is hardly any sunlight However, she found that her condition still bothered her considerably after her arrival there.

Teaching Points

1 Strong family history of allergy in this case.

2 Association with poison-ivy dermatitis.

3 Association with drug allergy.

4 Some cases of sunlight allergy are truly allergic and passive transfer is demonstrable.

5 Diagnostic procedures involve the mask method, in which the patient wears a mask during the daytime, or the dark-room test

SUMMARY

Physical allergy includes sensitivity to heat, cold, effort, and sunlight The manifestations may be those of urticaria and angioneurotic edema or asthma. The diagnosis is made from the history and trial exposure Treatment includes

avoidance, graduated exposure to offending agents, administration of belladonna, histamine, and occasionally histaminase.

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Miscellaneous Allergy

ALLERGIC HEADACHE; HISTAMINE HEADACHE; MIGRAINE
CASE REPORT
ALLERGY OF THE EYE
ALLERGIC VERTIGO
CASE REPORTS
LOEFFLER'S SYNDROME
CARDIOVASCULAR ALLERGY
GASTRO-INTESTINAL ALLERGY
GENITO-URINARY ALLERGY
ARTHRITIS
CASE REPORT
EPILEPSY
BLOOD DYSCRASIA
SUMMARY

Under this chapter heading are included some allergic manifestations which are not very common Space will not permit more than the mere mention of these conditions and the inclusion of some clinical case reports of each It should be observed that clinical allergy may be found in allergic individuals wherever the shock tissue or its derivative is present i e , the skin and mucous membranes

ALLERGIC HEADACHE, HISTAMINE HEADACHE, MIGRAINE

Migraine and Allergic Headache. It is established that headaches, usually of the migraine type, may occasionally be allergic This assumption is strengthened by the finding of the criteria for allergic diagnosis It would therefore be wise to subject a patient suffering with such headaches to

an allergic survey and treatment, especially if previous examination has revealed no cause for the headache, if other therapy is unsuccessful, and if the criteria for allergic diagnosis are present. In these instances it is thought that the basic change is either vasoconstriction or, more commonly, vasodilation of the meningeal vessels. This results in an edema of the meninges, and is due to sensitivity to allergens, usually foods. Fatigue, excitement, exertion, worry, foci of infection, and other factors contribute to the incidence, frequency, and severity of these headaches.

Treatment should include the usual measures employed in allergic therapy. In addition, belladonna and histamine may be given. Ergotamine, benzedrene sulfate, prostigmine, and oxygen inhalation may also be of value. Freedom from pain obtained from ergotamine tartrate in these cases may be due to the dilatation of the cerebral arterioles which it produces. The drug is effective sometimes when given by mouth At other times it must be given intravenously or hypodermically. The dosage is 0.25 to 0.5 mg. subcutaneously every two or three hours until relief is obtained.

Histamine therapy is of occasional value in allergic headaches. It is said that this therapy is of special value in the so-called histamine headache. This condition is associated with a marked positive intradermal reaction to histamine and certain characteristics which distinguish it from the migraine type of headache These include particularly the absence of an aura, of gastro-intestinal manifestations, and a marked reaction to cold This type of histamine headache, or vasodilating or erythromelalgic type of headache, presents a history of hemicrania The onset occurs rather late in life as compared with that of a typical migraine Paroxysms may be induced by the administration of histamine, and the headache may be relieved by the administration of adrenalin. It is accompanied by signs of local vasodilatation

such as sweating and flushing over the pain area. The pain may be relieved occasionally by pressure over the carotid or temporal artery; the pain frequently occurs when the patient lies down Because these patients are markedly sensitive to histamine it is best to start treatment with a very small amount of the drug, gradually increasing the dose. It is reported that relief has been obtained by such treatment in many instances The writer's experience has not been too encouraging in this connection.

Case Report

CASE 34. Patient, a young physician, came from an allergic family. He had been subject for many years to paroxysmal, unilateral headaches These headaches were preceded by an aura, and accompanied by nausea and vomiting. The paroxysm would last for 24 to 48 hours, during the course of which the patient would lie down in a darkened room (because of his photophobia) and abstain from eating, because the very odor or sight of food nauseated him At times the headaches were so severe that it was necessary to administer morphine He stated that he dreaded the approach of family reunions or of holidays because they always brought on these headaches, and he ascribed their occurrence under these circumstances to the prevailing excitement

Following recognition of the allergic nature of the headaches, an allergic survey was undertaken This revealed the patient to be markedly sensitive to chicken meat. Clinical trial corroborated the positive skin test The sensiti[illegible] so marked [illegible]

[illegible] food, such as soups, that might contain chicken stock. It was realized later that chicken was served at his home on holidays and at other celebrations, and for this reason these family dinners frequently ended so unpleasantly for the patient With the institution of an allergic diet, the headaches disappeared

an allergic survey and treatment, especially if previous examination has revealed no cause for the headache, if other therapy is unsuccessful, and if the criteria for allergic diagnosis are present. In these instances it is thought that the basic change is either vasoconstriction or, more commonly, vasodilation of the meningeal vessels. This results in an edema of the meninges, and is due to sensitivity to allergens, usually foods. Fatigue, excitement, exertion, worry, foci of infection, and other factors contribute to the incidence, frequency, and severity of these headaches.

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perience of the writer, indicating that inhalants and foods may play an important part in the development of this disease. In some of these cases the elimination of the offending agent brought about complete relief.

Iritis This may be due to focal infection, or it may be associated with urticaria or angioneurotic edema and migraine, in which case the cause may be an allergy to some exogenous substance.

Retinal Allergy. This is being more frequently recognized. There are many instances reported in the literature indicating the possibility that lesions such as retinal hemorrhages, retinal detachment, and macular edema may be of allergic origin. The writer has seen two instances of edema of the macula One, an elderly physician, presented a history of transitory attacks of blindness, accompanied by massive angioneurotic edema involving the face, lips, and fingers, following the ingestion of fish. Examination indicated the presence of edema of the macula of the left eye. With proper dietary restrictions, this edema cleared up and the vision improved

Another instance was also that of a physician, aged 35, who presented a definite history of allergy. This man had been suffering for many years with severe paroxysms of migraine headaches, usually following ingestion of chicken (vide supra) He developed transitory blindness due to edema of the macula of the right eye. An allergic survey revealed him to be *sensitive* to chicken meat and peanuts, and it was found that shortly before he had developed the attack of blindness, he had eaten some peanut-butter sandwiches Subsequent experience indicated that the headaches from which he suffered usually followed the ingestion of chicken With proper dietary treatment both the eye condition and the headaches disappeared entirely.

Optic Nerve Allergy. Allergic reactions of the optic nerve have also been reported These have followed the adminis-

Teaching Points:

1. Not all migraine types of headaches are allergic
2. When allergic, these headaches are usually due to food sensitivity.
3. Histamine therapy may be of value in the so-called histamine type of headache.

ALLERGY OF THE EYE

In addition to eye symptoms which accompany hay fever, allergic rhinitis, and allergic conjunctivitis, there are other clinical allergic manifestations of the eye which deserve mention. Instances of contact dermatitis of the eyelids due to nail polish and nail-polish remover, mascara, and orris root are not uncommon. Smears made from the secretions of the eye show a predominance of eosinophils The symptoms are usually relieved by the local application of epinephrine

Vernal Catarrh. This is thought by some to be allergic. Its seasonal occurrence would suggest the possibility of sensitivity to either pollen or fungi.

Episcleritis. Episcleritis, a paroxysmal condition accompanied by sudden onset of intense hyperemia and edema of the episclera, may be associated with migraine or angioneurotic edema. This condition has been thought to be allergic. It is associated with marked redness of the eye, tearing, and photophobia

Phlyctenular Keratoconjunctivitis. This has been shown to be due to tuberculin and food allergy It is frequently associated with other allergic manifestations In some patients the occurrence of this condition is definitely seasonal and suggests pollen sensitivity. It is accompanied by lacrimation and redness of the eye, and development of discrete gray or yellow opacities in the cornea, giving rise later in the course of the disease to scars in the center of the cornea. There have been many reported instances, one in the ex-

Corti Any irritation of the cochlea, the organ of Corti, the cochlear nerve branch, or its central nuclei in the brain will give rise to a hearing defect or to tinnitus. In a like manner any irritation of the end organ in the vestibule or the tracts of the vestibular nerve branch of the auditory nerve, or its central nuclei in the brain, will give rise to disturbance in equilibrium or dizziness.

It is evident, therefore, that any type of irritation, whether due to toxemia, infection, or edema in the internal ear or its associated nerve structures, will be accompanied by such symptoms as dizziness, tinnitus, and either partial or total deafness depending upon the extent and location of the lesion. Hence, involvement of the acoustic labyrinth gives rise to tinnitus and deafness while irritation of the vestibular portion of the internal ear and the semicircular canals gives rise to vertigo In labyrinthine vertigo, therefore, stimulation of the labyrinth either by turning or by caloric tests may show normal response between attacks and a delayed or no response during the attack.

The pathologic physiology of allergic vertigo can be explained probably on the basis of an edematous reaction in

[illegible] particularly Ménière's syndrome being caused by a process similar to that of angioneurotic edema and urticaria affecting the internal ear. Recent studies on the water balance of patients suffering with Ménière's syndrome indicate that reduction of fluid intake, the administration of a sodium-free diet, and ammonium chloride—in other words, an attempt at dehydration—gives many of them considerable relief from vertigo This would seem to indicate, at least indirectly, that the basic mechanism probably is one of edema It may account for the fact that many of these patients show some improvement from the administration of belladonna and epinephrine, as reported in

tration of foreign serum, or have been associated with migraine and angioneurotic edema. The writer observed one case of transient amblyopia and blurred disk which occurred following the ingestion of fish. Many other instances of a similar nature are reported in the literature.

ALLERGIC VERTIGO

Vertigo of allergic origin may occur either as a single isolated symptom or in conjunction with a series of other symptoms, such as tinnitus, deafness, and gastric manifestations. When found in association with these symptoms it is referred to as labyrinthine vertigo or Ménière's syndrome. *This consists of acute, sudden, paroxysmal attacks of dizziness* accompanied by tinnitus and various degrees of loss of hearing. During the attack the patient may break out in a cold sweat. The paroxysm may be severe enough to cause him to fall to the ground. The duration varies from a few minutes to a few hours. There may be accompanying nystagmus. The attack may be preceded or accompanied by nausea and vomiting. Tinnitus may be unilateral or bilateral and is as a rule high pitched The impairment in hearing is usually partial and temporary, returning to normal in the interval between attacks

A short review of the anatomy of the internal ear is essential to an understanding of the probable pathologic physiology of allergic vertigo. The internal ear is composed of the cochlea, the vestibule, and the semicircular canals. These form the membranous labyrinth which is located in a bony cavity commonly referred to as the bony labyrinth. The semicircular canals, or the organs of equilibrium, are supplied by the vestibular branches of the auditory nerve, whose end organs are found in that portion of the internal ear called the vestibule. The cochlea or the auditory portion of the internal ear is supplied by the cochlear branch of the auditory nerve whose end organs are the organs of

cent eosinophils The Wassermann reaction was negative and roentgen ray of the chest was negative. Allergic investigation showed definite positive reactions to tobacco, sweet potatoes, fish, glue, rabbit hair, dust, egg, chicken, tomatoes, potatoes, figs, pears, prunes, plums, grapes, and mushrooms This patient was observed and treated from 1935 to the present During these five years he had only two or three very slight attacks On one occasion the attack occurred after he helped clean the car with a vacuum cleaner which had no bag, and exposure to the dust gave him a severe attack of dizziness.

CASE 36. Patient, male, aged 56, was first seen in January At that time he complained of an eczematous skin

[illegible]

granulous character For the past few years he had been

[illegible]

negative The

The nose and

revealed him to be sensitive chiefly to kapok, horse dander, dust, barley, pyrethrum, eggs, chocolate, celery, parsley, lettuce, watermelon, buckwheat, asparagus, and prunes.

It is interesting to note the occasional association of attacks of vertigo in this patient with migraine-like headaches A review of a fairly large number of patients suffering with allergic headaches reveals quite a few who complain of severe attacks of vertigo and hearing disturbances. This would tend to indicate that the same mechanism—namely, pressure and irritation caused by localized edema in the brain, labyrinth, and meninges—may be responsible for both vertigo and headache.

The patient was instructed to follow a strict allergic diet. His fluid intake was reduced Extract of belladonna was administered and after a few months of treatment he began to improve The skin [illegible]

better and the [illegible] rably

he has been pr[illegible] that

[illegible] the

several instances. It is obvious that labyrinthine vertigo may result from causes other than allergy, as, for example, infections, tumors, toxemia, or hemorrhage in the internal ear or brain centers.

Adequate treatment is based on the elimination of offending factors and hyposensitization wherever indicated. Dehydration, sedation, eradication of foci of infection—all these measures have been used to advantage. Several instances of allergic vertigo have been observed by the author.

Case Reports

CASE 35. Patient, male, aged 24, was first seen in October, 1935, at which time he complained of paroxysmal attacks of dizziness. The first attack was in 1933; the second was in 1934. After that he had two more attacks in 1935. These attacks were characterized by a feeling of pressure in the back of the head, a sensation of buzzing and ringing in his ears, and marked dizziness so that he could hardly walk. Accompanying these attacks there were also deafness, tinnitus, and occasional vomiting. With each attack it was necessary for the patient to be confined to bed for three to four weeks. The last attack in 1935 continued for six or seven months

The patient was employed in a brokerage office and stated that his first severe attack of vertigo came on after he was engaged in licking stamps and envelope flaps on a large number of items that were to be mailed. Shortly after this work he became troubled with a tightening sensation in the throat and became quite dizzy.

Subsequently, it was found on skin testing that he was sensitive to sweet potatoes, from which stamp glue is made. He further stated that smoking aggravated his condition. On several occasions he experienced short periods during which he was troubled with paroxysmal sneezing and shortness of breath He had one cousin with hay fever and another cousin with eczema. A general physical examination was negative. Examination of the ears was negative The hearing was normal. The nose and sinuses were negative. The urine was negative. The blood count showed 9 per

performed on that day were entirely negative. It is inter-

Subsequently, positive reactions were obtained to eggs, milk, and pork, and a few weeks later another marked constitutional reaction developed following intradermal testing with parsley. This reaction was quite as severe as the reaction obtained from testing with garlic and was accompanied by vertigo, urticaria, and asthma necessitating administration of epinephrine over a period of several hours.

Teaching Points:

1. It would seem advisable to look into the possibility of an allergic etiology in any patient for whose dizziness no obvious cause is found, or in one whose vertigo is not improved following other forms of therapy.

2. The possibility of allergy playing an important etiologic role is especially likely if the patient has a positive family history of allergy, or gives a history of other allergic manifestations such as hay fever, asthma, or eczema, or shows a blood eosinophilia. On skin testing such a patient the physician is likely to obtain good positive skin tests which would further encourage the assumption of an allergic background.

LOEFFLER'S SYNDROME

This condition is a disease entity characterized by an afebrile course and the presence of respiratory symptoms. The roentgen ray of the chest shows definite infiltration of the lung. There is an eosinophilia which may be as high as

past year. He states that the only time he had any recurrence was after some dietary indiscretion.

CASE 37. Patient, male, aged 34, stated that he had been subject to attacks of dizziness for as long as he could remember. These attacks occurred several times a day and lasted for two or three weeks at a time. They usually were accompanied by some transitory decrease in hearing and culminated in a cold sweat. On occasions there was some loss of consciousness. Sometimes the patient passed out completely, and sometimes he was disturbed only to the extent that he felt like fainting. There were some accompanying manifestations such as eructations of gas and nausea He was seen for the first time in June, at which time he had been having attacks of dizziness, several times a day, over a period of a month. He had noticed that certain foods, such as pork, eggs, and milk, might bring on an attack. Over a long period of time he had tried the effect of addition or elimination of these foods from his diet and stated that he could definitely bring on a severe attack by drinking milk or eating pork or eggs or foods which might contain milk or eggs There was no family history of allergy

The general physical examination was entirely negative. There was no blood eosinophilia. The nose and throat examination was as follows: Cochlea· Audiogram revealed practically normal hearing in both ears except for dips at certain frequencies showing so-called islands of hearing defects of mild degree. Hearing in the left ear was a little better than in the right ear. There was absence of tinnitus at any time. Vestibular apparatus Irrigation of both ears with cold water gave normal responses. The tests showed normally functioning internal ears except for the hearing defects noted.

Skin sensitization tests were quite interesting. On the occasion of his first visit he was tested to about six allergens, one of which was garlic. About two or three minutes after these intradermal tests were done, the patient complained of generalized itchiness and a severe choking sensation. He [illegible] over his entire skin with severe large urti- [illegible] is breathing labored and [illegible] a very severe constitutional reaction to garlic, for the other skin tests which were

examination shows evidence of a necrotizing arteritis, some hypertrophy of the smooth muscle, and local perivascular eosinophilic infiltration. There is sufficient evidence suggesting that the etiology of the disease may be allergic.

GASTRO-INTESTINAL ALLERGY

The occurrence of gastro-intestinal manifestations resulting from the ingestion of foods to which a patient is sensitive is not uncommon Children are particularly prone to develop nausea, vomiting, and abdominal pain from foods to which they are allergic. If the food is an essential one, like milk or eggs, and the allergy is unrecognized, the parents are likely to insist that the child eat the food, and this may lead to a continuation of the allergic symptoms The patient may show other allergic manifestations, such as eczema or swelling of the lips, or a distressing cough after he eats such foods, and this association of symptoms may lead to the suspicion of dietary allergy. It is also possible to have occasional gastro-intestinal allergy as a result of inhaling the odor of foods or other substances. Acute abdominal symptoms may be due to allergy or, obviously, to other causes, but the possibility of allergic manifestations should not be excluded in doubtful cases, especially if the patient is otherwise allergic.

Common clinical manifestations of gastro-intestinal allergy are canker sores and lesions in and about the mouth. These may be due to the ingestion of certain foods or they may be due to drugs One patient developed very severe canker sores shortly after smoking a cigarette. This man was found to be sensitive to tobacco

Allergic lesions may occur anywhere in the gastro-intestinal tract. There is no reason why the same type of lesion that occurs in urticaria and involves the skin, or the same lesion that occurs in the nasal mucous membrane in hay fever, may not occur in the mucous membrane of the gas-

50 per cent. This syndrome has been referred to as Loeffler's syndrome and is thought by many to be allergic.

CARDIOVASCULAR ALLERGY

Reports have appeared from time to time attempting to show the possible role of allergy in the production of certain clinical cardiovascular conditions Thus, it is claimed by some that thrombo-angiitis obliterans is associated with and due to an allergy to tobacco. This is suggested by the large number of positive skin reactions obtained in such patients as compared with a similar group of controls The evidence points to the possibility of such allergy, although final proof has not as yet been presented

Several cases have been observed by the writer in which attacks of paroxysmal tachycardia have occurred in individuals who present the criteria for allergic diagnosis, and in whom the attacks seem to have been precipitated by the ingestion of certain foods.

The allergic reaction to a large extent involves smooth muscle, and the blood vessels are rich in smooth-muscle tissue. One would therefore suppose that the allergic reaction would be accompanied by an elevation in blood pressure. As a matter of fact, allergic manifestations such as bronchial asthma are most frequently accompanied by hypotension, and the acute allergic reaction similar to acute anaphylactic shock is accompanied not by an elevation but by a fall in blood pressure.

Periarteritis nodosa is not a common disease. It is characterized by a variety of symptoms including polyneuritis, gastro-intestinal symptoms, epigastric pain, renal symptoms, marked anemia, enlargement of the spleen, fever, leukocytosis, and loss of weight. This disease, as a rule, goes undiagnosed and as it may be accompanied by a rise in blood eosinophils, muscle tenderness, and soreness, is confused with possible trichinosis. The blood-vessel wall on

allergy. The proper interpretation of the effect of these diets on the patient's condition involves careful and prolonged observation and study.

GENITO-URINARY ALLERGY

Urinary-bladder involvement due to allergy to foods has also been described These patients have many of the symptoms of cystitis with tenesmus and dysuria, without any local findings. Further investigation may reveal an allergic background, and satisfactory improvement may follow allergic treatment

Menstrual disturbances have been noted in some instances to be due to allergic factors The best proof of the possibility of allergic manifestations in the uterus and its appendages may be derived from the fact that occasionally menstrual cramps result from a constitutional reaction following treatment with pollen extract Such a reaction occurring in a pregnant patient may even lead to miscarriage. Uterine manifestations are demonstrable by dysmenorrhea, change in the amount and duration of flow, and leukorrhea

ARTHRITIS

Reference is made in the literature to the role of bacterial and food allergies in the development of some forms of arthritic involvement This association is due to the fact that some allergic conditions, such as serum sickness and drug allergy, are frequently accompanied by joint symptoms. In serum sickness the joints may be enlarged, swollen, and painful The fluid obtained from these joints may show the presence of horse serum Cytologically, this fluid is identical with the exudate obtained from the inflamed joints of rheumatic fever, or from a truly allergic joint condition, namely, intermittent hydroarthrosis. The role of allergy in the genuine inflammatory arthritides, however, is not established

tro-intestinal tract. When these lesions do occur they give rise to many gastro-intestinal symptoms such as nausea, belching, gastric distress, vomiting, abdominal pain, and colitis. Some of these conditions go unrecognized or are diagnosed as a gastric neurosis. In many of these instances, gastro-intestinal x-ray series will indicate the presence of colonic spasm, segmentation of the small bowel, and gastric retention.

In some instances, allergy to foods may give rise to symptoms indistinguishable from those of cholecystitis. Such patients present no objective evidence of gallbladder disease and the gallbladder is found normal at the operating table.

Food allergy may result either in spasm of the bowel or in localized edema of the intestinal mucous membrane. This may produce spastic constipation or diarrhea Ulcer-like pain may also occur as the result of allergy to foods. Mucous colitis, especially if accompanied by other allergic manifestations, may be of allergic origin

The diagnosis of gastro-intestinal allergy involves first a careful medical study of the patient. An individual who presents a long-standing gastro-intestinal history is entitled to a complete physical examination and such laboratory studies as may be needed to rule out organic pathology This may include gastric analysis, roentgenograms of the gallbladder and of the gastro-intestinal tract, etc If these studies are negative, and particularly if the patient shows evidence of an allergic background, then one should consider the possibility of an allergic etiology.

The history may offer clues as to the possible foods which cause the patient's condition Food diaries may be helpful in this connection (see Table 5) Skin tests, unfortunately, are not too reliable, although when properly employed may occasionally throw some light on the diagnostic problem The elimination diets referred to earlier in this book are of great value in the etiologic diagnosis of gastro-intestinal

BLOOD DYSCRASIA

The most frequent normal response in allergic disorders is a blood eosinophilia. However, clinical sensitivity may manifest itself by definite changes in the blood picture.

Agranulocytosis. This condition is usually associated with septic sore throat, high fever, severe constitutional symptoms, and a marked decrease or total absence of granulocytes in the blood. Within the last 12 years there have appeared several hundred case reports of agranulocytosis due to the administration of drugs, such as amidopyrine, dinitrophenol, gold salts, sulfonamides, and acetphenetidin. These are instances of acquired sensitivity to drugs manifested by changes in the blood both in the bone marrow and in the periphery. Thiouracil may also cause granulocytopenia.

SUMMARY

Under the heading of miscellaneous allergy are included some allergic manifestations which are not very common but must be kept in mind.

Allergic headache and migraine may be of allergic origin. The clinical manifestations are typical. In addition to general allergic treatment, therapy includes the administration of belladonna, histamine, and ergotamine.

Allergy of the eye may have a wide variety of manifestations and includes allergic conjunctivitis, contact dermatitis of the eyelids, vernal catarrh, episcleritis, phlyctenular keratoconjunctivitis, iritis, retinal allergy, and allergy of the optic nerve.

Allergic vertigo may occur as a single isolated symptom or in conjunction with other symptoms grouped under the heading of Ménière's syndrome. This condition should be kept in mind in instances where the cause of vertigo has not been determined.

The writer has seen four instances of involvement of single joints such as the finger joints or the knee due to an allergy to foods and associated with giant urticaria.

Case Report

CASE 38. Patient, female, white, gave a positive family history of allergy. She had had several paroxysms of massive, severe, generalized urticaria in the last few years. The last attack was associated with excruciating pain and limitation of motion of the cervical vertebrae. Roentgen-ray study of this region was entirely negative The rest of the physical examination and laboratory studies were also negative. At this time, the patient developed another severe attack of urticaria and accompanying this attack there appeared a marked swelling of the middle joint of one of the fingers of the right hand. The joint was enlarged and there was definite limitation and pain on motion, but no redness or marked tenderness. The condition was reversible, appearing and disappearing within a few hours, and in a general way simulating the urticarial reaction. Roentgen ray examination of the involved joint was entirely negative.

This patient had been diagnosed as psychoneurotic. It was obvious, however, in spite of psychotherapy, hospitalization, and other forms of treatment, that she was not improving. An allergic survey revealed her to be sensitive to many foods and her condition subsided following institution of allergic treatment.

EPILEPSY

Several instances of epileptiform convulsions or convulsive variant are on record which have been relieved by the removal of offending foods from the patient's diet. While the temptation is great to infer from these observations that idiopathic epilepsy may often be allergic, the evidence at hand does not warrant such an assumption. It would seem that in individuals who are otherwise allergic, food allergy may act as a contributory factor.

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Loeffler's syndrome is an allergic manifestation.

Cardiovascular allergies are not definitely established

Gastro-intestinal allergy resulting from the ingestion of *foods is not uncommon. The diagnosis is made from the* history, from intradermal tests, and from elimination and trial diets. The treatment as a rule is successful.

Genito-urinary allergy involves the urinary bladder, and as a rule is due to the ingestion of foods to which the individual is sensitive.

*Arthritis is occasionally found as an allergic manifesta*tion An example of this condition is hydroarthrosis

Epilepsy and epileptiform convulsions may be on an al*lergic basis.*

Agranulocytosis may be an expression of drug allergy.

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Allergy in Children

INCIDENCE
ALLERGIC PROBLEMS IN THE PRACTICE OF PEDIATRICS
CASE REPORTS
COMPLICATIONS OF ALLERGY IN CHILDREN, THE NEED FOR EARLY DIAGNOSIS
CASE REPORTS
TREATMENT
SUMMARY

INCIDENCE

One cannot overemphasize the importance of the early recognition and treatment of allergic conditions in children It is conservatively estimated that at least 10 per cent of infants and children at one time or another are in need of allergic treatment The onset of allergy may occur at any age in a child or infant It is associated as a rule with a positive antecedent family history of allergy

ALLERGIC PROBLEMS IN THE PRACTICE OF PEDIATRICS

Proper diagnosis involves *recognition* of the allergic state and the determination of the etiologic factors producing the child's allergy Following is a review of some of the more frequent clinical allergies found in children in order to emphasize their importance and management.

Case Reports

Heredity and Allergy in Children.

CASE 39 Patients, females, aged 2 This set of identical twins give a positive family history of allergy At the age of

Todd, T. W., M. B. Cohen, and B. H. Broadbent: The role of allergy in the etiology of orthodontic deformity (abstract), Jour. Allergy, 10:246, 1939.
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INCIDENCE

One cannot overemphasize the importance of the early recognition and treatment of allergic conditions in children. It is conservatively estimated that at least 10 per cent of infants and children at one time or another are in need of allergic treatment. The onset of allergy may occur at any age in a child or infant. It is associated as a rule with a positive antecedent family history of allergy.

ALLERGIC PROBLEMS IN THE PRACTICE OF PEDIATRICS

Proper diagnosis involves recognition of the allergic state and the determination of the etiologic factors producing the child's allergy. Following is a review of some of the more frequent clinical allergies found in children in order to emphasize their importance and management.

Case Reports

Heredity and Allergy in Children

CASE 39 Patients, females, aged 2 This set of identical twins give a positive family history of allergy. At the age of

eight months, both received one grain of aspirin for a cold and shortly afterward developed urticaria and wheezing It was also found that neither twin could eat eggs without developing some skin involvement. Intradermal tests showed both to be positive to eggs.

Teaching Points:

1. It is agreed by most observers that the development of the atopic group of allergic disorders is governed by heredity. As a matter of fact, the presence of a family history of asthma, hay fever, or eczema is presumptive proof that the child's condition is probably also allergic.

2. The hereditary nature of allergy was emphasized recently in a report by the author of similar allergies occurring in seven sets of identical twins. These twins had positive family histories of allergy and presented similar allergic conditions.

Bronchial Asthma and the Allergic Cough.

CASE 40 Patient, female, aged 4. This child had a persistent paroxysmal, dry cough for the first two years after birth. Her mother stated that it was thought at first that the child had frequent chest colds for which no possible cause could be found. Later on the cough became more severe and was associated with wheezing At times it would last for two to three days and would be accompanied by high fever, so that the diagnosis of pneumonia would be made. She had been cured of six such attacks The child had never been able to take cow's milk and presented serious feeding problems in infancy Many milk substitutes were tried in order to avoid allergic manifestations She was also markedly sensitive to dust Her attacks of asthma were especially severe in the early summer when she was taken to the lake where her parents had a cottage. Investigation revealed her to be sensitive to milk, dust, fungi, and a few other substances. Suitable changes in the child's environment and diet, together with treatment with extracts of molds, brought about a therapeutic result that was excellent

Teaching Points:

1. Bronchial asthma is frequently preceded in infants and children by an unexplainable persistent cough which occurs in paroxysms In the absence of any demonstrable cause, such as an enlarged thymus or mediastinal glands, it is well to think of the possibility of its being allergic.

2. Because the paroxysms are associated with some bronchitis and fever, the diagnosis of pneumonia is often made. But the attack lasts only one or two days and is relieved by ephedrine and epinephrine.

3 The possibility of sensitivity to molds and fungi, as well as to pollen, should be kept in mind if the history indicates seasonal asthma In the case reported above, it was quite suggestive. While closed during the winter, summer cottages become dusty and mildewed due to increased humidity and lack of ventilation.

4 This infant presented serious allergic feeding problems The resources of the pediatrician are taxed in such cases, for he must be familiar with all the ingredients of the numerous proprietary baby foods.

5 In the case of breast-fed babies, he must keep in mind the possibility of the infant being sensitive to some food ingested by the mother and passed into mother's milk in quantities sufficient to produce symptoms in the baby.

Hay Fever and Pollen Asthma

CASE 41 (See Fig 37) Patient, male, aged 11 This boy had had seasonal asthma and hay fever since the age of three [illegible]
the sp[illegible]
showed [illegible] trees, grasses, and ragweed Pollen treatments given annually for the past five years brought about the disappearance of the asthmatic condition

Teaching Points:

1 It should be pointed out that children can tolerate the same dosage of pollen as adults



Fig. 37 "Allergic salute" observed as a common mannerism in children presenting nasal allergy such as hay fever.

2 No child is too young to take pollen treatments.

3. The annual treatment for hay fever is most desirable.

4 In many instances, children who have taken annual treatment for a few years can get along well without treatment

5. What is even more important, the treatment of hay fever in children is an effective prophylactic measure against the development of bronchial asthma. Many children with untreated hay fever begin to develop asthmatic symptoms toward the end of the pollen season, and if this early warning goes unheeded, the child will continue to have asthma for increasing intervals after the season is over. Before very long, the patient has bronchial asthma which occurs throughout the year.

6 The boy mentioned in the above case report experienced occasional itchiness of the nose which developed in him certain mannerisms so characteristic in some allergic children "Sniffing," nose-rubbing, and nose-wrinkling are some of these mannerisms The boy rubbed his nose as may be seen in Fig 37, in characteristic fashion, pushing the tip of the nose upward and inward in an attempt *not only* to relieve his itching but also to spread the nasal walls and in this manner to secure better nasal ventilation This peculiar characteristic and common allergic *mannerism* has been termed "the allergic salute"

Allergic Rhinitis and Conjunctivitis.

Case 42. Patient, female, aged 12 This young girl gave a history of allergic rhinitis and some pollen hay fever of several years' standing. The nasal discharge was thin, watery, and rich in eosinophils There was no evidence of any infection of the paranasal sinuses Investigation showed her nasal symptoms to be due to allergy to pollen and some other substances

In addition, and particularly during the past few years, she had been troubled with a severe *conjunctivitis* involving the right eye especially. This was manifested by itching

and lacrimation, invariably brought on and made worse when exposed to crowds, such as at church or at the movies. There was a family history of allergy. Intradermal tests with human dander extract were negative. She gave a positive direct test and a positive passive transfer test to an extract of orris root. A conjunctival test was also markedly positive to orris root.

Teaching Points:

1. Allergic rhinitis is not uncommon in children.

2. It is perennial and is frequently mistaken for colds.

3. However, examination fails to reveal infection in the nose.

4. The nasal secretions are thin, watery, and rich in eosinophils.

5. The nasal mucous membrane has a typical boggy, bluish-gray appearance.

6. Paroxysmal conjunctivitis may or may not be allergic in origin. The vernal catarrh type which is seasonal is thought by some to be allergic. Some instances of vernal catarrh have been shown to be due to pollen sensitivity

7. There is a type of conjunctivitis which is definitely allergic as indicated in the above-reported case. The eyes are red and itchy and the discharge shows many eosinophils. The cause, as a rule, is an inhalant such as animal danders, dust, or orris root. The last of these is a frequent offender because it is found commonly in most cosmetics

Infantile Allergic Eczema, Flexor Eczema. This condition shows a typical distribution in infants and children. As the child becomes older, the lesions are found mostly on the flexor surfaces of the elbows and knees, on the face and neck, and occasionally on the wrists. The characteristic lesion in infants is a vesicle. The characteristic lesion in childhood is a papule. In childhood, the condition is called flexor eczema of allergic origin As the dermatitis becomes more and more chronic, there appear secondary skin

changes—the skin becomes thick and leathery due to lichenification and hyperkeratosis. The characteristic symptom is pruritus. Severe nervous manifestations also develop. The treatment consists in the elimination of the offending factors, prevention of scratching and skin trauma, local applications, and sedation

CASE 43 Patient, male, aged 3½. This child had flexor eczema (allergic) and urticaria. The lesions were papular and involved the face, flexor surface of the elbows, and popliteal spaces. There [illegible]
asthma [illegible]
hair bro [illegible]
the child to be markedly sensitive to wheat and wheat products, oranges, wool, and goat hair Marked improvement followed the elimination of these factors.

Teaching Points:

1 This is an instance illustrating the possibility that inhalants (in this case wool and mohair) may cause urticaria. This boy could not ride in a train or automobile unless the coach or automobile seat was completely covered with a rubber sheet, and even then he would develop urticaria.

2 Hospitalization will relieve the acute skin manifestations in most instances, because the change in environment removes from the patient most of the substances to which he is sensitive

Another case of infantile eczema illustrative of many teaching points in connection with this subject may be found at the end of Chapter 9.

Urticaria and Angioneurotic Edema. This condition occurs frequently in children Foods are the most frequent cause, although occasionally inhalants may also bring on an attack. This condition is not serious unless it involves the glottis There seems but little doubt that in the case of children who are good swimmers and are allergic to cold, fatalities which have resulted while in swimming are due

and lacrimation, invariably brought on and made worse when exposed to crowds, such as at church or at the movies. There was a family history of allergy. Intradermal tests with human dander extract were negative She gave a positive direct test and a positive passive transfer test to an extract of orris root. A conjunctival test was also markedly positive to orris root.

Teaching Points:

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may be evidenced by the occurrence of severe nasal or asthmatic symptoms and may even prove fatal.

2 It is for this reason that caution must be exercised in the administration of drugs to allergic children. Parents should be warned not to give the allergic child any home remedies without the physician's specific permission.

3 Similarly, the child suffering with an allergic skin condition may be made worse by the very ointment which is given for relief. This in many instances is due to an acquired specific sensitivity to the ingredients of the ointment Such allergy should be ruled out by patch-testing before proceeding with the use of the suspected ointment.

COMPLICATIONS OF ALLERGY IN CHILDREN; THE NEED FOR EARLY DIAGNOSIS

The early recognition and treatment of the allergic state in children is important not only because of the therapeutic results, but also in order to prevent complications. Contrary to the belief of some, children do not usually "outgrow" their allergy, even though in a few instances there may be a spontaneous loss of sensitivity. In other instances, a child may become symptom-free, merely because of an accidental change in environment or diet. As a rule, in spite of wishful thinking and endless temporizing, if untreated the allergic child continues to suffer This frequently leads to complications and secondary changes which make difficult the solution of a problem which was comparatively simple in the beginning In this way untreated nasal allergies become complicated by the appearance of nasal polyps, the occurrence of nasal infection, and the development of facial and dental deformities Bronchial asthma develops into emphysema, chest deformities, and bronchiectasis. Skin allergies lead to secondary changes such as keratosis and lichenification The continuation of allergic symptoms over a long period of time affects the

not to drowning but to edema of the glottis. Postmortem examination in these cases shows no water in the lungs Case reports illustrative of this condition may be found at the end of Chapter 9.

Contact Dermatitis (Paint).

CASE 44. (See Fig 25) Patient, female, aged 5. This child presented a vesicular dermatitis over the back of her thighs There was considerable itching and oozing. The family history was negative for allergy. Patch tests with a small amount of powdered scrapings obtained from the toilet seat were markedly positive.

Teaching Points:

1. This is an instance of acquired allergic dermatitis due to contact, and is similar to poison ivy dermatitis.

2. It may result from contact with plant oils, chemicals, dyes, and other substances which either penetrate the skin easily or dissolve in the oil of the skin.

3 Sensitivity is demonstrable by the use of the patch test.

4. Treatment is largely symptomatic and must include the avoidance of the cause.

Drug Allergy.

CASE 45. Patient, male, aged 12. This patient had an allergic rhinitis and hay fever for the past five years He stated that after taking one-half of an aspirin tablet for a headache about three years ago, he was suddenly seized with a severe attack of asthma and generalized urticaria, for the relief of which two injections of epinephrine were administered. One year later he was given some "cold" tablets with the same result He had refused to take any medicine since that time.

Teaching Points:

1. The manifestations of drug allergy may be slight or severe. They may include a mild dermatitis and slight fever (acquired sensitivity), or in an atopically allergic child they



FIG. 38 Facial deformity in long-standing allergy of upper respiratory tract.

child's growth, health, and personality. He loses weight and becomes irritable, fretful, and sleepless. He misses school, cannot play with other children, and frequently finds it difficult to learn a trade which will help him obtain and hold some gainful occupation.

Case Reports

Facial Deformities.

CASE 46. (See Figs. 38 and 39.) Patient, male, aged 12. This boy presented a history of seasonal hay fever and allergic rhinitis over a period of six years. The attacks were very severe. There was marked nasal obstruction. Nasal examination showed the presence of polyps. The family history was positive for asthma As an infant he had had considerable trouble with his skin. He was sensitive to house dust, ragweed, orris root, and wheat.

Teaching Points:

1. Nasal and respiratory allergies in early life frequently lead to bony changes in the base of the skull, to a narrowing of the arch of the palate (the so-called Gothic arch), to a depression of the bony prominence of the cheek bones, so that they assume a flat appearance.

2. These changes in turn lead to a crowding of the incisor teeth, with the result that many of these children need corrective measures, including dental braces.

Chest Deformities.

CASE 47. (See Figs. 40 and 41.) Patient, male, aged 14. This boy presented a history of severe bronchial asthma which started during his first year of life He had had flexor eczema. His mother had hay fever Examination showed evidence of pulmonary emphysema and also of marked deformity of the chest.

Teaching Points:

1. This instance is presented to illustrate pulmonary emphysema and chest deformities as one of the complications



Fig. 38 Facial deformity in long-standing allergy of upper respiratory tract.

of untreated bronchial asthma. The clavicles, instead of sloping down toward the sternum, assume a horizontal position.

2. In many instances, as may be seen in this case, there is an anterior bulging of the sternum, giving rise to a "pigeon breast" deformity.



FIG. 39. Dental deformity in long-standing allergy due to arching of hard palate.

Chronic Bronchitis and Bronchiectasis.

CASE 48. Patient, female, aged 10. She had had paroxysmal attacks of choking, coughing, and wheezing, accompanied by profuse expectoration and an elevation of temperature, for several years. Roentgen-ray examination of the chest using iodized oil showed no evidence of tuberculosis. There was definite thickening of the bronchi and bronchioles.

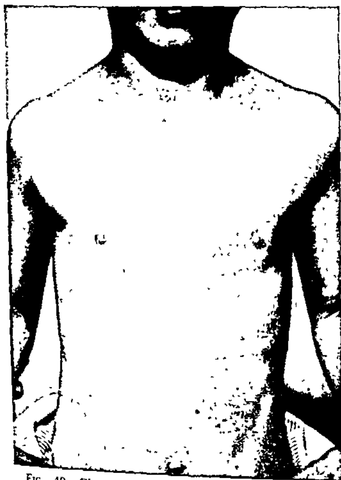


Fig. 40. Chest deformity following long-standing asthma, in boy aged 14.



Fig. 41. Lateral view of same patient as shown in Fig. 40

Teaching Points:

1. Chronic suppurative bronchitis and bronchiectasis may follow long-standing untreated bronchial asthma in children.

2. It is not an uncommon complication and is responsible for the constant elevation of temperature in these patients.

3. It is an example of a situation which could have been handled rather easily in the beginning. However, after infection sets in, successful treatment is much more difficult.

TREATMENT

The adequate treatment of allergic disorders in children is predicated primarily on the early, accurate, and complete etiologic diagnosis. Little or nothing therapeutically worth while is to be expected from some single procedure such as tonsillectomy, ionization, iodized-oil insufflation, and the like. Much, however, can be done for these children through patient, painstaking care. Such care is obtained only through proper teamwork of pediatrician and allergist, teamwork which to be effective must extend through the period of diagnosis as well as the period of treatment. The improvement to follow will earn for the attending physician the parents' everlasting gratitude.

SUMMARY

Early recognition and early treatment of allergic conditions in children are essential. The prophylactic and curative value of such treatment is impressive. Children do not, as a rule, "outgrow" their allergy. If not treated, allergies in children may become complicated by the appearance of nasal polyps, the occurrence of nasal infection, the development of facial and dental deformities, emphysema, bronchiectasis, and chest deformities. Skin allergies lead to secondary changes such as keratosis and lichenification. The

continuation of allergic symptoms affects the child's growth, health, and personality. The proper management of allergy in infants and children involves attention to feeding problems and a knowledge of the numerous proprietary baby foods. Otherwise the diagnosis and treatment are identical with that employed in the management of adults.

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17

Diagnostic Skin Tests

THE SCHICK TEST (DIPHTHERIA)
THE DICK TEST (SCARLET FEVER)
THE SCHULTZ-CHARLTON TEST (SCARLET FEVER)
THE CASONI TEST (ECHINOCOCCUS DISEASE)
THE PERTUSSIS SKIN TEST
THE TUBERCULIN TEST
THE FOSHAY TEST (TULAREMIA)
THE BRUCELLERGIN TEST (UNDULANT FEVER, BRUCELLOSIS)
THE MALLEIN TEST (GLANDERS)
THE ITO-REENSTIERNA REACTION (CHANCROID)
THE FREI TEST (LYMPHOGRANULOMA INGUINALE)
THE TYPHOIDIN TEST (TYPHOID FEVER)
THE COCCIDIOIDIN TEST (PULMONARY COCCIDIOIDOMYCOSIS)
SUMMARY

This chapter includes a brief discussion of the skin tests which are generally employed as an aid to clinical diagnosis, most of which tests have an allergic basis

THE SCHICK TEST (DIPHTHERIA)

The basis for this test is not allergic, but it so much resembles the rest of the skin tests which follow that it was thought desirable to include it in this chapter.

Technic. 0.1 cc. to 0.2 cc. of a saline solution containing a measured amount of diphtheria toxin is injected (1/50 of a m.l.d.) intradermally into the flexor surface of the forearm. A control test is done with the heated Schick material.

Reading the Reaction. A positive reaction consists in the appearance at the point of injection of an area of erythema, infiltration, and induration. The reaction occurs within 24

to 36 hours after the inoculation, reaches a peak within *four to five days, and lasts about seven to nine days.* It should be read in six to nine days. If the erythematous area exceeds 0.3 cm. in diameter, the reaction is said to be positive. Pressure will not cause the erythema to disappear. Occasionally one may obtain a pseudo-reaction. This occurs however within a few hours, lasts for only two to three days, and is not followed by brown pigmentation. For these reasons, *it is necessary to carry out a control test,* which should cause no reaction at the site of injections

Interpretation. If the individual is immune to diphtheria, he possesses diphtheria antitoxin in his serum. The toxin injected intradermally during the Schick test is therefore neutralized by the circulating antitoxin so that no local reaction occurs. A negative reaction (the absence of erythema) therefore indicates that the individual tested is immune to diphtheria. Conversely, a positive reaction indicates the lack of such immunity, and therefore the need of toxin-antitoxin or toxoid administration. The test is also *of value in determining the need for immunization of an* individual who has been exposed to the disease. The test should be repeated annually.

THE DICK TEST (SCARLET FEVER)

Technic. 0.1 cc. of Dick test toxin is injected intradermally into the forearm of the patient The injection is made with a tuberculin syringe and a 26-gauge needle. These are sterilized by boiling in distilled water. No control is usually necessary, for the amount of protein in the testing material is very small

Reading the Reaction. *A positive reaction consists in the* appearance of an area of erythema which is one centimeter or more in diameter, and is not accompanied by induration as is the case in the Schick test. The reaction should be

read 24 hours after the test is performed. It lasts 48 to 72 hours The reaction is considered negative if the area of erythema is absent or is less than one centimeter in diameter, and if it disappears at the end of 24 hours.

Interpretation. An individual who does not possess an immunity to scarlet fever will, upon being injected with scarlet fever toxin, show an erythema or positive reaction While this test is not so reliable as the Schick test, it does indicate the presence or absence of susceptibility to scarlet fever The Dick test usually becomes negative after the first week of scarlet fever. However, during an attack of the disease, if the reaction remains persistently positive, it is presumptive evidence against the disease being scarlet fever For example, an individual may have a negative Dick test and still have scarlet fever at the time the test is performed. There are many reservations, therefore, in the interpretation of the test.

THE SCHULTZ-CHARLTON TEST (SCARLET FEVER)

Technic. 0.1 cc of scarlatinal streptococcal antitoxin or 0.5 cc of convalescent scarlet fever serum is injected intradermally into the center of an erythematous lesion of a patient who is suspected of having scarlet fever

Reading the Reaction. A positive reaction consists in blanching of the area of erythema within six to 20 hours after the injection. This blanching is due to the neutralization of the toxin in the skin by the antitoxin which is injected

Interpretation The test is of value only within the first day or two of the disease A negative test does not necessarily mean that the condition is not scarlet fever. A positive test, however, is a definite indication of the presence of the disease.

THE CASONI TEST (ECHINOCOCCUS DISEASE)

Technic. 0.01 to 0.02 cc. of a 1-1,000, or 1-10,000 dilution of the sterile antigen is injected intradermally into the forearm of a patient suspected of having echinococcus disease. The same type of test may be employed in a similar manner with respective antigens for the diagnosis of present or past infestation with filariasis, ascariasis, trichinosis, and bilharziasis

Reading the Reaction. The appearance of an immediate wheal with or without pseudopods and surrounded by an area of erythema indicates a positive reaction This wheal appears within 10 to 15 minutes following the test. Occasionally, the reaction is of the delayed type, and may last from 24 to 72 hours.

Interpretation. An immediate reaction is usually diagnostic, although positive reactions have been obtained in individuals who have had no such infestation, and negative reactions have been observed in individuals who are so afflicted.

THE PERTUSSIS SKIN TEST

Technic. A small amount of the endotoxin or the Sauer vaccine is injected intradermally into the arm or forearm of a patient who is suspected of having pertussis in the early stage of the disease.

Reading the Reaction. The reaction is positive if wheals and erythema occur at the point of inoculation.

Interpretation. The basis for the reaction is an acquired hypersensitiveness or allergy to the causative agent and its product. This allergy is induced within eight to ten days of the onset of the disease and disappears toward the end of its course. The test may be helpful as a diagnostic aid in doubtful instances of pertussis

THE TUBERCULIN TEST

Tuberculin allergy (see Fig 42) has been discussed in detail in a previous chapter. Use is made of our knowledge of this form of allergy in testing an individual for evidence



Fig 42 Positive patch test to tuberculin (Vollmer test) Note negative control in center.

of tuberculous infection, past or present, active or inactive, acute or chronic

Technic. Among the tests based on local allergic manifestations the following may be mentioned the scratch test of von Pirquet, the intradermal test of Mantoux, and the ophthalmotuberculin test of Calmette. It has been shown recently that the purified protein derivative of tuberculin (P P D) can be used intradermally to great advantage in the diagnosis of tuberculosis The intradermal test, using old tuberculin, is done by injecting 0 1 cc. of a dilution of 1:10,000, and reading the reaction 48 hours later. A dilutio-

of 1-1,000, and in the same dose may be used if the first test is negative.

The Vollmer patch test for tuberculin allergy is used by some, although it is not so accurate as the intradermal test. It consists in the application to the skin of a small patch of material impregnated with tuberculin. The technic is essentially the same as that of the patch test employed for *the diagnosis of contact dermatitis. This test is easy and* simple to perform A control test is also done with inert material, in order to rule out allergy to the adhesive.

Reading the Reaction. The tuberculin reaction is a delayed reaction, occurring in 24 to 48 hours and manifesting itself by an area of induration and erythema at the point of inoculation followed by brown pigmentation. The Vollmer test is said to be positive if there appear at the point of contact numerous vesicles or papules on an erythematous base, and if the control, which is usually in the center, is negative.

Interpretation. The intradermal tuberculin test is the most accurate, although the patch test is easier and quicker to perform. A positive tuberculin reaction is an indication of a state of allergy to tuberculin. It shows that the individual has had or has now a tuberculous lesion Because most people fall into this group, it is clear that tuberculin reactions may be positive in most adults and hence are of limited clinical significance Since such infections do not occur until later in life, the reaction assumes added importance if found positive in infants or in young children. A negative tuberculin reaction, however, is of great clinical value, for it indicates the absence of clinical, active, or healed *tuberculosis.*

THE FOSHAY TEST (TULAREMIA)

Technic. 0.01 cc. of a suspension of heat-killed organisms is injected intradermally into the arm of a patient suspected of having tularemia.

Reading the Reaction. A positive reaction consists in the pearance of an indurated, raised erythematous area with pale center simulating very much a positive tuberculin st This reaction reaches its height in about 48 hours after e onset of the disease, and lasts for a few days Toward e end of the period of reaction there is a small area of rown pigmentation.

Interpretation. It is a specific test for *Pasteurella tularen-s* The positive test does not necessarily mean active ılaremia The test persists for several years after the in-ection has subsided It is an indication of a tuberculin type f hypersensitiveness. If a negative test becomes positive it s a definite indication of the presence of tularemia, par-ticularly if undulant fever can be ruled out

THE BRUCELLERGIN TEST (UNDULANT FEVER, BRUCELLOSIS)

Technic. 0 1 cc of either a vaccine of the Brucella organism or of a chemically treated suspension of Brucella, referred to as brucellergin, is injected intradermally into a patient suspected of having undulant fever. The vaccine as a rule is diluted 1-10. Brucellergin, however, is considered a little more reliable because it is more accurately standardized

Reading the Reaction. A positive reaction usually develops in from 24 to 48 hours and consists of an area of erythema and induration at the point of injection extending from 1 5 to 5 or 6 cm in diameter.

Interpretation. The test indicates either past or present infection with the Brucella organism. It is fairly accurate. In some instances the injection of this material stimulates the formation of agglutinins For this reason, the agglutination test should always be done prior to the performance of the skin test

THE MALLEIN TEST (GLANDERS)

Infection with *B. mallei* (*Malleomyces mallei*) in animals and in man leads to a tuberculin type of hypersensitiveness so that positive skin reactions have been obtained in infected animals and in the human injected with mallein. Other diagnostic procedures, however, are used more widely and more satisfactorily in the diagnosis of the disease in the human.

THE ITO-REENSTIERNA REACTION (CHANCROID)

The infection with *B ducreyi* (*Hemophilus ducreyi*) may be diagnosed by intradermal injection with a suspension of the killed bacteria or with the diluted pus. The reaction appears late in the disease and the allergy lasts for many years.

THE FREI TEST (LYMPHOGRANULOMA INGUINALE)

Technic. 0.05 cc. of diluted pus obtained from the local lesion is injected intradermally. There are now available commercially purified antigens for this purpose. It is therefore preferable to inject a small amount of such an antigen intradermally.

Reading the Reaction. This is made in 48 to 72 hours. A subject with lymphogranuloma will show an erythematous papule surrounded by a zone of erythema of varying size and intensity

Interpretation. Reactive papules of less than 6 mm. in diameter are considered negative, as are nonerythematous wheals Strongly positive reactions yield papules surrounded by vesicles or pustules Subsided reactions leave faintly pigmented areas.

THE TYPHOIDIN TEST (TYPHOID FEVER)

The typhoidin test is a diagnostic skin test performed by the intradermal injection of an extract of typhoid bacilli. It is similar to the tuberculin reaction, and indicates an acquired allergy based on past or present infection. However, it has so many limitations that it is not of great clinical value

THE COCCIDIOIDIN TEST (PULMONARY COCCIDIOIDOMYCOSIS) *

Technic. "Coccidioidin as prepared by Smith is used, and 0.1 cc dilution of 1 100 and 1 1,000 is injected intracutaneously by means of new tuberculin syringes and small gauge needles The control is 0 1 cc of 1:10 dilution of the Bureau of Animal Industry synthetic medium injected in a similar manner."

Reading the Reaction. "Readings are made at 24, 48, and 72 hours and the results recorded in millimeters of erythema and induration Reactions of 5 mm. or more at 48 hours are considered positive"

Interpretation. "A negative test usually excludes the possibility of infection, whereas a positive test is indicative of past or present infection"

SUMMARY

The above tests indicate the capacity of the skin to react as an immunologic organ Elsewhere in the book repeated references are made to the reactivity of the skin in cases of sensitivity to infestation with *intestinal* parasites and fungi In most instances these skin tests are based on the presence of bacterial allergy resulting from the original infection Infections other than those mentioned in this chap-

* Goldstein, D M, and J B McDonald Pulmonary coccidioidomycosis, Jour Amer Med Asso, 124 559, No. 9 Feb 26 1944

ter are also accompanied by the development of skin reactivity, although its character and the presence of other more reliable tests render it less important as a diagnostic aid. Mention is made of a few of these tests not because of their diagnostic value but because they are of interest in connection with the study of allergy.

In moniliasis or oidiomycosis a positive skin reaction (inflammatory) may result from testing with oidiomycin. This reaction resembles the tuberculin type of reaction.

Sporotrichosis is associated with the development of a tissue allergy which manifests itself in a delayed, tuberculin type of skin reaction to sporotrichin The absence of previous or present infection with the fungus will yield a negative skin reaction.

Bacterial sensitivity manifests itself by skin reactivity of the tuberculin type also in other infections, such as leprosy, although the test has not been clinically developed.

Intradermal testing with *leishmanin* gives a positive delayed reaction in leishmaniasis in individuals who have had or have the disease.

Tissue changes and skin allergy are associated with various other bacterial agents such as the *staphylococcus*, the *pneumococcus*, the *meningococcus*, and the *streptococcus*.

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